Fetal Alcohol Syndrome in South Africa: prevalence, risk factors and prevention

Michael F. Urban

Doctoral Thesis submitted to the Faculty of Medicine and Health Sciences, Ghent University

September 2017

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PREFACE

Fetal alcohol syndrome (FAS) and the teratogenic effects of prenatal alcohol exposure more broadly constitute a known but under-estimated public health problem in South Africa. FAS impacts on children's development, on the people who care for them, and their communities more broadly. It is aggravated by the broader impact of alcohol on families, but should also be considered as a problem in its own right.

This thesis advocates for society, and the health system specifically, to take on a more active stance in the fight against FAS. The thesis describes the prevalence of FAS in several different environments across sites in two South Africa provinces, and interprets the implications regarding prevalence in other South African environments and risk groups. The focus is broadened by a description of the effects of prenatal alcohol exposure in cases without syndromic FAS features. The prospects for prevention are then discussed. For several sites, drinking patterns of mothers are described, as well as how these change during and after pregnancy, and other risk factors are identified. Finally a health promotion-based intervention study is presented, together with lessons regarding the role of awareness-raising and educational activities in reducing the burden of FAS on society.

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LIST OF ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
AEP	Alcohol Exposed Pregnancy
AIDS	Acquired Immune Deficiency Syndrome
ALD	Alcohol dehydrogenase
ARBD	Alcohol Related Birth Defects
ARND	Alcohol Related Neurodevelopmental Disorder
AUD	Alcohol Use Disorder
BAC	Blood Alcohol Concentration
BC	before Christ
BDMP	Birth Defects Monitoring Program
BMI	Body Mass Index
BSA	Black South African
CD	Congenital Disorder
CDC	Centers for Disease Control and Prevention
CHW	Community Health Worker
DALY	Disability Adjusted Life Year
FARR	Foundation for Alcohol Related Research
FAS	Fetal Alcohol Syndrome
FASD	Fetal Alcohol Spectrum Disorder
GDP	Gross Domestic Product
GMDS	Griffiths Mental Development Scales
GMDS-ER	GMDS-Extended and Revised
GQ	General Quotient
HIV	Human Immunodeficiency Virus
ICD10	International Classification of Diseases, version 10
IMR	Infant Mortality Rate
IOM	Institute Of Medicine
IPV	Intimate Partner Violence
IQ	Intelligence Quotient
ND-PAE	Neurobehavioral Disorder associated with Prenatal Alcohol Exposure
NIAAA	National Institute on Alcohol Abuse and Alcoholism
PAE	Prenatal alcohol exposure
PFAS	Partial Fetal Alcohol Syndrome
P/FAS	FAS and partial FAS (combined)
PFL	Palpebral Fissure Length
SAC	South African ‘Coloured’

SES	Socio-Economic Status
TLFB	Timeline Follow-back
USA	United States of America
WHO	World Health Organization

ARTICLES

1. **Urban M**, Chersich MF, Fourie L, Chetty C, Olivier L, Rosenthal J, Viljoen D. Fetal alcohol syndrome among grade-one children in the Northern Cape Province: prevalence and risk factors. *South African Medical Journal* 2008; 11: 877-882. PMID: 19177895

2. **Urban MF**, Olivier L, Viljoen D, Lombard C, Louw JG, Drotsky L-M, Temmerman M, Chersich MF. Prevalence of fetal alcohol syndrome in a South African city with a predominantly Black African population. *Alcohol: Clinical and Experimental Research 2015; 39(6):1016-26*. PMID: 25941030

3. Olivier L*, **Urban M***, Chersich MF, Temmerman M, Viljoen D. Burden of fetal alcohol spectrum disorders in the rural West Coast of South Africa. *South African Medical Journal 2013; 103(6): 402-405*.DOI:10.7196/SAMJ.6249. PMID: 23725961 (*Equal first author)

4. **Urban MF**, Olivier L, Louw JG, Lombard C, Viljoen DL, Scorgie F, Chersich MF. Changes in drinking patterns during and after pregnancy among mothers of children with fetal alcohol syndrome: A study in three districts of South Africa. *Drug Alcohol Depend.* 2016 Nov 1;168:13-21. doi: 10.1016/j.drugalcdep.2016.08.629.

5. Chersich MF, **Urban M**, Olivier L, Davies L, Chetty C, Viljoen D. Universal prevention is associated with lower prevalence of fetal alcohol spectrum disorder in Northern Cape, South Africa: a multicentre before-after study. *Alcohol and Alcoholism*, 2012; 47(1):67-74. PMID: 22037537

6. Davies L, Dunn M, Chersich M, **Urban M**, Chetty C, Olivier L, Viljoen D. Developmental Delay of Infants and Young Children with and without fetal alcohol spectrum disorder in the Northern Cape Province, South Africa. *African Journal of Psychiatry* 2011; *14: 299-305.*

7. Davies L-A, Cockcroft K, Olinger L, Chersich M, **Urban M**, Chetty-Makkan CM, Turnbull OH, Olivier L, Viljoen D. Alcohol exposure during pregnancy alters childhood developmental trajectories in a rural South African community. *Acta Paediatrica*, epub ahead of print, July 2017 DOI:10.1111/apa.13978

CHAPTER 1: INTRODUCTION

1.1 A BRIEF HISTORY OF ALCOHOL USE

Archaeological, chemical and plant genetic evidence indicate that humans have intentionally brewed alcohol for millennia. Chemicals absorbed in pottery jars suggest that alcohol was produced and stored in Henan province in China from ca. 7000-6600 B.C. [1], the brewing of beer from barley is recorded in the written history of ancient Egypt and Mesopotamia and of wine production in in the 'fertile crescent' as of 6000 B.C. [2].

Although alcohol was brewed in part to preserve fluids for later use, the psychoactive and pleasurable aspects of drinking lent itself to a **social and cultural role**. In the ancient Mediterranean cultures it was used for cultural roles as diverse as the symposia described by Plato and religious rites in the Judeo-Christian tradition [3]. Individual drinking cultures led to social mores regarding acceptable alcohol use, some cultures advising regular moderate use and others more tolerant of binge drinking.

Alcohol played a role in the workplace even in ancient times. The workers or slaves who built the pyramids, and the Roman legionaries, received sizable daily rations of wine [3].

The increasing scale of alcohol production associated with the industrial revolution led to an intersection of the effects of alcohol and of broader social conditions. During the well-publicised London gin epidemic of 1720 – 1751, consumption of cheap imported gin by the urban poor was blamed for social problems including crime and social unrest. However, modern interpretations suggest that poverty and inequality were the primary driver of the social problems, which may have been exacerbated by alcohol [4].

Many traditional societies used alcohol of one sort or other. In Africa alcohol has historically been brewed from palm wine and grains such as sorghum. Sorghum beer with an alcohol content of 1-2% has been brewed in many parts of Africa, including by several tribes in southern Africa, and has an important traditional role [5].

Some societies, including Native Americans in New England, indigenous Australians, and the Khoisan group of western South Africa did not have an alcohol tradition [6]. The abrupt introduction of alcohol into these societies led to dramatic social problems.

1.2 ALCOHOL RELATED HARM

1.2.1 Terminology related to drinking

The effect of an amount of a particular type of alcohol is related to the amount of pure alcohol it contains. This can be expressed as the number of **'standard drinks'**, or in this document just as 'drinks'. The amount of pure alcohol in a standard drink varies considerably by country, from 10-15g of pure alcohol. For purposes of this study we use a pragmatic definition related to alcohol in 330ml of beer (~14g pure alcohol), or the equivalent amount of wine or spirits [7]. In general there are no harms that are specific to the type of alcoholic beverage consumed unless it contaminated in some way.

Unlike other drugs, low levels of alcohol use may have modestly beneficial health effects [8], although higher levels of drinking are associated with a risk of alcohol-related harm. **A threshold is therefore applied to differentiate 'low risk' from 'risky' (or 'hazardous' or 'heavy') drinking**. The threshold is expressed in standard drinks, and differs between men and women. It is lower in women because women on average have lower lean body mass and smaller liver capacity to metabolize alcohol, which results in higher blood alcohol concentration for the same alcohol intake.

The United States National Institute on Alcohol Abuse and Alcoholism defines **low-risk drinking** in women as being no more than 7 standard drinks per week or 3 drinks per session. This threshold is not relevant in all situations, for example in pregnancy

there is no defined risk threshold and any alcohol should be considered risky, especially in the first trimester [9].

Risky drinking is defined as drinking that may cause dependency or other alcohol-related harms. This may be due to the ongoing heavy drinking often associated with dependency, or due to heavy episodic or binge drinking. In women risky drinking is considered to be more than 7 standard drinks per week or alternatively 4+ drinks in a session [10]. The latter is referred to as **heavy episodic drinking** or more commonly as **binge drinking**.

An alcohol use disorder (AUD) has been variously defined by the World Health Organization (WHO) International Classification of Diseases version 10 (ICD10) [11] and the American Psychiatric Association 5th Diagnostic and Statistical Manual [12]. I will restrict myself to a brief description of the ICD10 definition, which describes an AUD as drinking that causes alcohol dependence or other harms to physical (for example cirrhosis) or mental health that are directly related to alcohol consumption [11].

Alcohol dependence is a cluster of behavioural, cognitive and physiological phenomena that develop after repeated alcohol use and that typically includes a strong desire to drink alcohol, difficulties in controlling its use in the face of harmful consequences, increased tolerance to its effects and sometimes physiological withdrawal symptoms [11]. Alcohol use that causes harm may be described as **harmful drinking**. The presence of alcohol-related harm does not presuppose alcohol dependence.

1.2.2 Alcohol related harms

The range of alcohol-related harms is wide, and includes health effects as well as secondary social, psychological and occupational effects [6].

Health harms include disorders that are strongly related to alcohol use, such as dependency and cirrhosis of the liver. The topic of this study, fetal alcohol syndrome (FAS), is a severe harm for which alcohol is considered a necessary cause.

In addition to being associated with its own health end-points, alcohol is also an intermediate factor in the causal chain for many diseases. It

is a component cause of over 200 adverse health outcomes including interpersonal violence and accidents, infections such as tuberculosis and Human Immunodeficiency Virus (HIV) or Acquired Immune Deficiency Syndrome (AIDS), and non-communicable diseases such as hypertension, stroke and several cancers [6,13]. Many of these disorders are common in South Africa – this includes not only the infectious diseases but also non-communicable diseases, which are increasing rapidly in prevalence.

There are also a wide range of potential psychosocial harms of drinking. Social effects may include loss of friendships, relationships, domestic violence, stigmatization and marginalisation [6]. Psychologically, depression is known to be associated. Socio-economic harms may include loss of work; or where earnings are low it may further impoverish the drinker's family or even community [14].

1.2.3 Factors associated with alcohol related harm

Alcohol-related harm may result from alcohol dependence, toxic effects on organ systems, or from the effects of intoxication (see Figure 1). These in turn relate to both the overall volume of alcohol consumption and the pattern in which it is consumed. The binge drinking pattern has specific risks including accidents, injuries or other violence due to intoxication. In addition, binge-drinking by pregnant women is a particular risk for FAS, as will be discussed later.

Drinking volumes and patterns vary greatly between and within societies. For example, alcohol consumption rates tend to be markedly lower in poorer than wealthier societies [14]. Within a society, alcohol use is often lower in those of low than high socio-economic status (SES) [16]. Drinking is usually lower in women than men [17], although in many societies there is a trend to increasing drinking among women [18].

There is evidence that the risk of harm per unit alcohol is not uniform across the population, with the risk being modified by a range of 'vulnerabilities' that increase the potential harm associated with a given level of drinking [6]. Vulnerabilities include family history of alcohol use, extremes of age, low SES or less economically developed society, and particular culture or ethnicities. Family history

of alcohol related harm is an important determinant of risk, although it is unclear whether the vulnerability is genetic or related to familial drinking patterns [6].

Figure 1: Drinking and alcohol-related harm

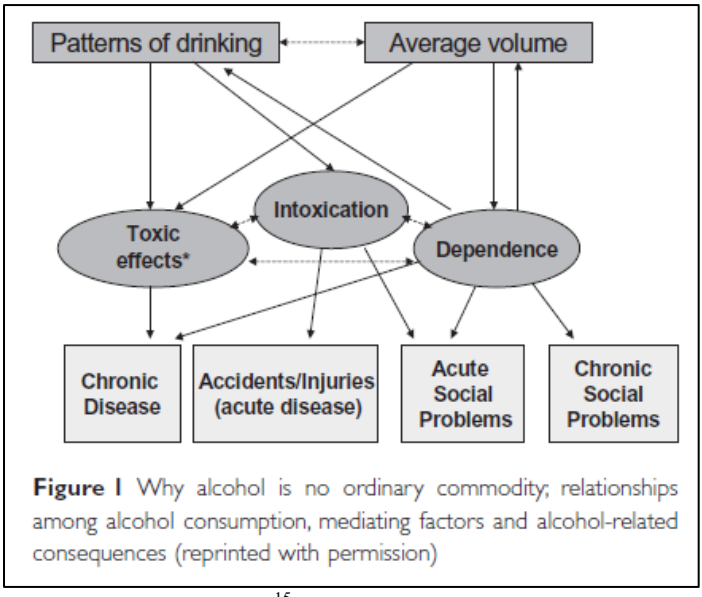


Figure 1 Why alcohol is no ordinary commodity; relationships among alcohol consumption, mediating factors and alcohol-related consequences (reprinted with permission)

(From: Babor *et al*, 2010 [15])

Alcohol related harms disproportionately affect those of lower SES, despite average alcohol use often being lower than among those of higher SES. For example, a meta-analysis showed that the odds of mortality being due to an alcohol-related cause was 1.5-2-fold higher in both men and women of low than higher SES [19,20]. It is thought that low SES is associated with multiple reasons for increased alcohol-related harm, including less safe environments, less extensive support networks, patterns of drinking that may include more abstinence, but also more binge drinkers. Similarly, drinkers in less developed societies experience more harm than those in developed countries [21].

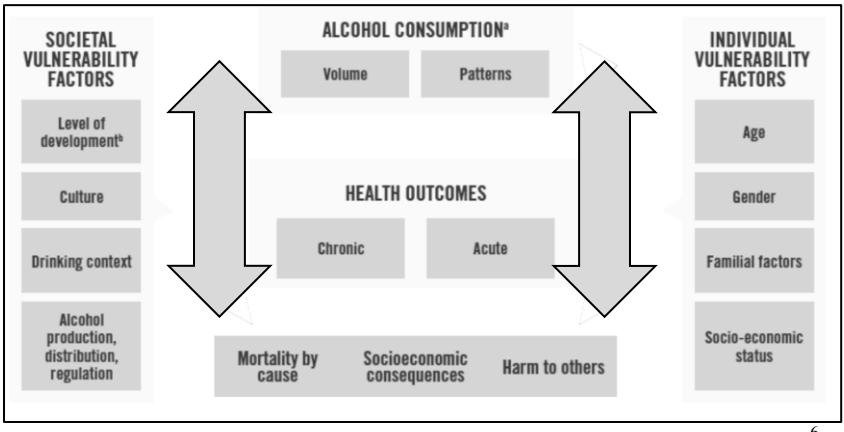
Although women generally drink less than men, this is partially offset by the fact that women have a greater risk of harm from a given amount of alcohol and the fact that the fetus of a pregnant woman can be affected [6].

Disparities in alcohol drinking patterns, as well as the harm experienced per drink, may vary between population groups and different ethnic groups [22]. Studies of health disparities between ethnic groups in the United States of America (USA) indicate that African-American drinkers experience greater negative effects than their Caucasian counterparts, despite later onset of drinking and drinking levels that are lower or comparable to their white counterparts [23].

The WHO Global Status Report on Alcohol and Health 2014 [6] proposes a conceptual model for the link between alcohol consumption, other vulnerabilities (both at individual and societal level) and adverse health outcomes (Figure 2). The more vulnerabilities a person has, the more likely the person is to develop alcohol problems [14]. Clustering of risk factors in some population groups, such as social exclusion, low income, malnutrition, cramped housing and poor access to health services may be as important as the alcohol exposure itself [24].

As a uniquely alcohol-related harm, FAS may relate to both drinking patterns and other vulnerabilities of pregnant women. Following a description of FAS, I will discuss both the drinking patterns and the other vulnerabilities/risk factors that increase the risk of having a child with the condition.

Figure 2: Conceptual model for causes of alcohol-related harm



(From: WHO Global Status Report on Alcohol and Health, 2014 [6])

1.2.4 Epidemiology of alcohol-related harm

Quantifying the role of alcohol as a cause of morbidity and mortality is complicated by the very wide range of health outcomes that it impacts upon, and the fact that for many adverse health outcomes it contributes only a component of risk, and is not often reported at the direct cause of death or disability.

Rehm *et al* [25] estimated that 3.8% of all deaths and 4.6% of disability is related to alcohol. In addition they calculate that alcohol-related costs (both health and social costs) contribute >1% of GDP in middle income countries. In developed countries, 12.8% of healthcare costs are attributable to alcohol use.

More recently Lim *et al* [26] estimated that in 2010 the three leading risk factors for global disease burden were high blood pressure (7.0%), tobacco smoking (6.3%) and alcohol use (5.5%). In addition, alcohol is in the top five risk factors for disease throughout the world. Importantly, it is believed that there has been a major increase in the contribution of alcohol between 1990 and 2010, with it ranking shifting from sixth to third leading cause of disease burden globally. Conversely, the contribution of poor water and sanitation, and of micronutrient deficiencies, has significantly diminished between 1990 and 2010.

The WHO Global Status Report on Alcohol and Health [6] estimates that in 2012 alcohol caused 3.3 million death (5.9% of global deaths), and 139 million disability-adjusted life years (DALYs) (5.1% of global disease and injury).

1.2.5 Epidemiology of Alcohol related harm in South Africa

A range of studies indicate that alcohol is a major contributor to morbidity and mortality in South and southern Africa. Mayosi *et al* [27] and Mayosi *et al* [28] discuss the effects of four 'colliding epidemics' in South Africa, namely HIV and tuberculosis, chronic non-communicable disease and mental health, and maternal and child health conditions. While child mortality in particular has benefitted from progress in addressing HIV, the risk factors for non-

communicable diseases have steadily increased in the two decades since the inception of democracy. The authors identified an urgent need to reduce harmful alcohol use, given the causal links between alcohol and other major health risks in the country, such as unsafe sex, HIV infection, tuberculosis, liver disease, mental illness, and injury. However, they make no specific mention of FAS.

The above-mentioned study of Lim *et al* [26] found that in 2010 alcohol was the leading risk factor for ill health in southern Africa (as well as in Eastern Europe and most of Latin America). However, it should be noted that the indicators used did not estimate the role of unsafe sex, which is a deficiency given that the high prevalence of HIV/AIDS in South and southern Africa.

An earlier study of the burden of disease in South Africa [29] found unsafe sex to be the largest contributor in the year 2000, with alcohol as fourth largest risk factor for death (7.1% of all death were attributable to alcohol) and third largest for disability (7.0% of all DALY's were attributable to alcohol). These authors estimated FAS to be the third leading cause of alcohol-attributable disability after AUDs and inter-personal violence; as a result they highlighted FAS as a priority area.

Whether the differences in ranking of alcohol as a risk factor for ill health reflect only difference in study methods, or also are indicative of secular trends between 2000 and 2010, is uncertain. There is certainly direct evidence for increased alcohol consumption in South Africa, at least in some demographic groups. For example Ramsoomar and Morojele [30] describe an increase in risky alcohol use e.g. binge drinking increased in SA adolescent females between 1998 and 2008.

The WHO [6] estimated that the fraction of deaths and of disease/injury attributable to alcohol in South Africa in 2012 was in the 5-9.9% range. This is second highest band, with only the former Eastern Bloc countries being in a higher range.

Alcohol is estimated to cost South Africa R37.9 billion annually [31]. This estimate includes costs of health care, crime and social welfare, alcohol treatment and prevention and road traffic accidents. It excludes less tangible costs such as premature morbidity and mortality, and absenteeism from work.

As a result of the various lines of evidence showing alcohol to be a considerable social and health burden, the South African government has targeted a reduction of per capita alcohol consumption of 20% by 2020, primarily by introducing a range of broad policy measures.

1.2.6 Congenital disorders and their epidemiology

A congenital disorder (CD), also known as a birth defect, is a condition affecting body structure or function that arises before birth. CDs are a diverse group of conditions that range from structural problems of individual organs (e.g. congenital heart defects) to disorders of enzyme function. Aetiologically they vary from 'multifactorial' conditions (the result of multiple underlying genetic and environmental causes), to specific genetic or chromosomal disorders, to those caused by teratogens. Teratogens are chemicals or other agents that cause CDs by exerting a toxic effect on the morphological and neurological development of the embryo and fetus. FAS, then, is a CD that results from the teratogenic effect of prenatal exposure to alcohol.

As a group, the CDs are increasingly understood to be a significant cause of morbidity and mortality. They are recognised in 2-3% of infants [32], and if conditions that usually present later in childhood (such as FAS) are included, CDs are estimated to affect 4-8% of children globally [33]. The role of CDs in morbidity and mortality is underestimated for several reasons: they often go undiagnosed, or deaths may be ascribed to a primary cause such as pneumonia rather than to underlying causes such as a CD. As a result their true extent as a cause of mortality and morbidity remains controversial [34–36].

There is agreement that in many middle income countries such as South Africa, the relative importance of CDs is increasing as these societies go through a 'health transition' due to changes in socio-economic, education, infrastructure and healthcare development. These shift society from a 'pre-industrial' state with high fertility and limited life expectancy to a 'developed' state with low fertility and long life-expectancy [37]. This shift is initially mediated by a reduction of infectious disease mortality in childhood. In this context, non-communicable diseases, which include most CDs, become more important contributors to morbidity and mortality.

Malherbe *et al* [38] show that South Africa is in the midst of transition, as reflected in the infant mortality rate (IMR). In 1993 the IMR was 45.1/1000 and, despite an increase related to the HIV epidemic, it has since improved to 33.5/1000 by 2013. The authors argue that at this IMR level CDs should receive attention. This is reinforced by their estimate that the country has a particularly high prevalence of teratogenic CDs, predominantly related to the teratogenic effects of alcohol. They suggest that up to 20% of all CDs may be teratogenic in origin, approximately double the global estimate [33].

The WHO has recognised the relevance of CDs, by adapting Millennium Development Goal 4, which focuses on reducing child mortality: the General Assembly of the WHO in 2010 [39] adopted a resolution to "redress the limited focus to date on preventing and managing birth defects, especially in low- and middle-income countries".

1.3 TEMPORAL TRENDS IN DRINKING

1.3.1 Trends in female drinking internationally

The WHO Global Status Report on Alcohol and Health (2014 edition) [6] provides information regarding drinking trends in 2010, and shows significant differences in alcohol use between different regions and countries. The annual alcohol per capita consumption in the African region (6.0 litres absolute alcohol/year) is in the mid-range, considerably lower than Europe, the continent with the highest per capita consumption (10.9 litres absolute alcohol/year) and much higher than the Eastern Mediterranean region (0.7 litres absolute alcohol/year). Unlike most other African countries, South Africa and neighbouring southern African countries Namibia and Zimbabwe were found to have significant alcohol problems.

Worldwide, women drink considerably less than men [40]. However, the difference in drinking between genders varies considerably between countries, suggesting that differences are in part historical and cultural. In recent decades female drinking has been increasing in some Western societies [41], a trend that has been attributed to changing gender roles [42]. In South Africa, a similar trend has been noted, with an increase in binge drinking by young women detected between 1998 and 2008 [30].

To explore comparative levels of drinking further, Table 1 presents a comparison of WHO national drinking statistics for South Africa, the USA and Belgium. South African women are twice as likely to abstain, and are less likely to be dependent on alcohol, but have double the per capita alcohol consumption. This suggest that the average female drinker in South Africa drinks at least 4 times more than her counterpart in the USA or Belgium, most often in a binge drinking rate (as reflected in the 'risky pattern of drinking' score).

It should be noted that national drinking patterns may not be applicable to different social strata and population groups within a society. For example, Kuntshe *et al* [43] compared different European countries and found that a country's level of gender equity and

strength of social welfare systems appeared to modify the way that personal education, employment and marital status interacted with alcohol use [43]. As will be discussed South Africa has its own unique mix of drinking patterns, many of which can be traced to its colonial past.

Table 1: Selected drinking data in 3 countries

	South Africa		United States of America		Belgium	
	Men	**Women**	**Men**	**Women**	**Men**	**Women**
Ever drank	72%	45%	94%	83%	96%	91%
Current drinkers-past 12 months	56%	26%	75%	63%	84%	80%
Alcohol per capita– drinkers only (litres pure alcohol/ year)	33.8	16.0	18.1	7.8	17.8	7.8
Alcohol use disorders (dependence and harmful use)	10%	1.5%	11%	4.2%	9%	3.0%
Alcohol dependence	4%	0.7%	7%	2.6%	5%	1.6%
Risky pattern of drinking score (maximum=5)	4		2		1	

(Adapted from WHO Global Status Report on Alcohol and Health, 2014 [6])

1.3.2 Trends in female drinking in South Africa

Details of female drinking trends in South Africa are provided in Table 2, which is adapted from the results of four large national surveys conducted in 1998 [44], 2003 [45], 2005 [46] and 2008 [47]. There was some variation in the results between studies that may represent trends, but could equally represent different study methods – for

example binge drinking was not defined in the same way for all studies.

The studies concur that only a minority of women drink. This is true in virtually all segments of the South African female population, whether it is stratified by age, province, urban versus rural residence, population group (with the exception of white South African women), or educational level.

The drinking trends by age show that both 'current drinking' and binge drinking increased with age during the reproductive years, except in the last study. It is unclear whether this represents a trend towards earlier drinking, and follow-up is important.

The provinces studied in this thesis are the Western Cape and Northern Cape. It is notable that across all studies these provinces had the highest, or near the highest, rates of current drinking and binge drinking, although some other provinces also had relatively high levels of drinking.

In all studies, urban women had higher rates of current drinking and binge drinking than rural women, although among rural women a higher proportion of drinkers were binge-drinkers.

By population group, women designated (by the South African census) as white South African were more likely to be current drinkers, but the population group designation South African Coloured (SAC) were more likely to be binge drinkers.

Regarding education attainment, the studies showed women with higher educational attainment tended to drink more, but that among those with limited education a higher proportion of drinkers were binge drinkers. The trend for overall binge drinking was unclear.

It should be noted that these national surveys do not have enough detail to capture drinking practices in specific high-risk areas. For example, a community household survey in five areas of the Cape Winelands district of the Western Cape previously described to have high rates of FAS found higher rates of female drinking: 66% were current drinkers, 49% had a binge drink in the past week and group binge drinking was the norm [48]. Nevertheless, the national data

suggest that the problem of FASD could extend well beyond the Cape Winelands.

National surveys may also exclude important subgroups. People living with HIV/AIDS now constitute a large and important subgroup of the South African population. In 2015 the estimated number of South Africans with HIV was 6.19 million people, including 22.7% of all reproductive age women. Of note is that HIV disproportionately affects the majority Black South African (BSA) population group: for example in 2012 the estimated rate of HIV positivity was 22.7% for adult BSA compared to 4.6% of the SAC group [49].

HIV-positive women are potentially a risk group for FAS, given the known links between alcohol and unsafe sex [50]; and between alcohol use - especially binge-drinking - and the risk of incident HIV infection [51]. A study of alcohol use by adults attending HIV clinics in Cape Town, which included 1051 females who were of predominantly BSA background, found a 32% rate of hazardous or harmful drinking [52].

Table 2: Percent drinking for women - by age, residence, province, population group & educational status

	1998 (DHS)		2003 (DHS)	2005 (SABSSM II)		2008 (SABSSM II)	
	Current drinking % in past month	**3+ Binge** % of all (% of drinkers)	**% current drinkers** % in past year	**% current drinkers** % in past month	**Binge*** % of all (% of drinkers)	**% current drinkers** (Past month)	**Binge*** % of all (% of drinkers)
AGE							
15-24	8.5	2.6 (30.0)	14.7	11.6	2.8 (24.7)	9.4-12.9	2.6-3.0 (26%)
25-34	15.6	5.1 (33.1)	14.7	13.9	3.6 (25.7)	20.5	6.0 (29%)
35-44	20.9	6.6 (31.7)	19.6	17.4	3.2 (18.2)	21.4	4.2 (19.6%)
45-54	23.4	8.2 (35.2)	13.4	22.5	4.5 (19.6)	20.0	2.9 (14.5%)
55-64	20.5	6.2 (30.6)	17.0	20.8	3.6 (17.3)	16.6	2.6 (15.7)
65+	16.9	5.0 (29.6)	12.2	14.4	1.9 (20.6)	11.6	1.5 (12.9)
PROVINCE							
Western Cape	24.2	**7.2** (29.6)	28.8	39.1	**9.5** (24.3)	33.1	**6.8** (20.5)
Eastern Cape	16.2	5.3 (33.0)	10.5	9.8	1.9 (19.3)	12.4	3.4 (27.4)
Northern Cape	23.1	**11.0** (47.6)	29.3	20.2	**5.2** (25.8)	33.6	**7.0** (20.8)
Free State	24.5	7.2 (29.4)	21.0	9.8	2.1 (21.5)	14.0	2.7 (19.3)
Kwazulu-Natal	11.5	4.2 (36.2)	3.6	9.1	1.7 (18.6)	8.2	1.2 (14.6)
Northwest	17.0	7.1 (42.1)	18.2	15.0	4.6 (30.7)	20.4	4.2 (20.6)
Gauteng	20.6	4.5 (21.9)	21.0	24.9	4.4 (17.7)	26.8	6.4 (23.9)
Mpumalanga	14.2	6.6 (46.5)	8.3	15.0	1.2 (8.0)	13.8	4.3 (31.2)
Limpopo	8.6	3.9 (45.4)	11.3	5.0	0.9 (18.1)	6.4	1.1 (17.2)

	1998 (DHS)	2003 (DHS)	2005 (SABSSM II)	2008 (SABSSM II)			
	Current drinking % in past month	**3+ Binge** % of all (% of drinkers)	**% current drinkers** % in past year	**% current drinkers** % in past month	**Binge*** % of all (% of drinkers)	**% current drinkers** (Past month)	**Binge*** % of all (% of drinkers)
RESIDENCE							
Urban	19.2	**5.6** (29.0)	19.5	22.0	**4.2 (19.1)**	22.6	**4.7 (20.8)**
Rural	13.2	**5.1** (39.0)	8.3	7.6	**2.0 (26.0)**	8.5	**2.3 (27.1)**
POPULATION GROUP							
Black African	**12.3**	5.1 (42.1)	11.4	**7.9**	**1.9 (24.0)**	10.0	**2.9 (29.0)**
BA urban	12.8	5.2 (40.7)	14.2				
BA rural	11.8	5.1 (43.5)	7.5				
SA Coloured	**23.2**	**7.9 (34.2)**	27.7	**30.0**	**9.8 (32.7)**	33.3	**10.4 (31%)**
White	50.5	7.1 (14.0)	50.9	51.2	6.5 (12.7)	61.7	5.9 (9.6%)
Indian/Asian	9.0	0.0	24.4	12.2	0.9 (7.4)	15.2	0.3 (2.0%)
EDUCATION							
No education	22.9	8.8 (38.6)	13.9	13.2	3.4 (25.6)	13.3	4.3 (32.3)
Grade 1-5	16.3	7.3 (44.6)	12.8	10.4	4.2 (40.3)	11.1	2.8 (25.2)
Grade 6-7	13.2	5.9 (44.9)	12.4	12.1	3.6 (29.7)	9.1	2.5 27.5)
Grade 8-11	12.7	4.1 (32.5)	14.9	10.6	2.2 (20.8)	21.4	3.7 (17.3)
Grade 12	18.5	3.4 (18.3)	14.2	22.5	3.9 (17.3)	61.7	5.2 (8.4)
Higher	33.4	4.2 (12.6)	32.6	36.7	4.4 (12.4)	52.5	3.5 (6.7)

*Based on AUDIT score
Adapted from: [44–47]

1.3.3 Trends for in-pregnancy drinking internationally

It is instructive to examine drinking in pregnancy, and also to link this to changes in public awareness of the risks of alcohol use in pregnancy. There is limited South African data available, but it is well documented in the USA. Therefore, data for the USA is summarised before returning to the South African situation.

In 1981 the US surgeon general issued a warning that no amount of alcohol could be considered safe in pregnancy. Following this there was increasing public concern about FAS and the effects of drinking in pregnancy, probably in excess of the existing evidence regarding low level drinking at the time. Armstrong and Abel [53] describe the resultant public movement as a 'crusade' and a 'moral panic'. Nevertheless, it appears to have had a significant effect on reported drinking practices.

Surveillance data from 21 US states between 1985 and 1988 [54] found that drinking by non-pregnant women remained steady at around 55%. Half as many pregnant women drank (25%), and drinkers drank about half as much alcohol in pregnancy. Of note, drinking by pregnant women declined steadily from 32% in 1985 to 20% in 1988, although there was no decline among less educated women or those under 25 years of age.

By comparison, surveillance data for the period 1991 to 2005 show that the prevalence of drinking by non-pregnant women remained similar to the 1980s (any drinking 55%, binge drinking 12%). By the start of the surveillance period, drinking in pregnancy had reached considerably lower levels (any drinking 12%, binge drinking 2-3%), but remained at a stable level throughout the surveillance period [55].

It was also found that recognition of pregnancy occurred at similar gestation in drinkers and non-drinkers – with 70% recognising it by 6 weeks and >90% by 12 weeks; 80% stopped drinking at this time and the remainder reduced significantly [56]. This is supported by other USA data from 2002-2007 that shows a rapid fall-off in prevalence of drinking in the first trimester of pregnancy, and a progressive reduction thereafter: prevalence of current drinking was 63% in non-

pregnant women, and then 19%, 7.8% and 6.2% in the first, second and third trimester respectively [57]. The same study noted that within 3 months after a pregnancy 32% of women were drinking, suggesting that many women restarted shortly thereafter.

Compared to 1991-2005 period, current surveillance data in the USA suggest that the prevalence of current drinking has stabilised among both non-pregnant women (53.6%) and pregnant women (10.2%). Women who binge-drink are less likely to quit in pregnancy [58,59], explaining the higher proportion of women who drink in versus outside of pregnancy [60].

There is evidence for significant differences of in-pregnancy drinking between population groups, although this too may have changed with time. Floyd *et al* [56] found that peri-natal drinking was twice as common in non-Hispanic Caucasian women than other ethnic groups, but Tenkku *et al* [61] found that these women were also more likely to reduce drinking in pregnancy. They found that pre-pregnancy drinkers who were Hispanic, Asian/Pacific Islander, African American or Native American women were much more likely to continue than were non-Hispanic whites, especially if they were binge drinkers. The authors suggested a need for targeting of interventions to reduce in-pregnancy drinking towards particular groups. More recently Tan *et al* [60] reported only modest differences of in-pregnancy drinking between population groups.

In some sub-populations the prevalence of drinking and binge-drinking during pregnancy is much higher. For example, a recent study found that up to 60% women in an Inuit community continued drinking in pregnancy [62].

Taken together the above data suggest that many women are drinking in the peri-conceptional period, and that in the absence of awareness of the risks of drinking in pregnancy, many women continued to drink throughout pregnancy. Significant reductions in prevalence of ongoing drinking in pregnancy have occurred over time. This may reflect changes in awareness or social acceptability of drinking. Nevertheless, a proportion of women continue drinking, and ongoing drinking is more common for binge-drinkers. It may vary between ethnic groups and in specific populations. A high proportion of women recommence drinking shortly after pregnancy.

1.3.4 In-pregnancy drinking in South Africa

The only national data for alcohol use in pregnancy is from the above-mentioned SABSSM II national survey of 2005, which included data from 894 pregnant women [46]. Nationally, risky drinking was present in 2.5% of pregnant women, compared to 6.2% of all women. In-pregnancy drinking was more common in urban dwellers (4.1%), the SAC population group (11.6%), and the Northern Cape Province (24.9%). In the Western Cape, the Northern Cape and the SAC ethnic group, risky drinking was less reduced in pregnant than in all women compared to other groups.

A number of surveys of drinking in pregnancy have been conducted across a wide range of sites and populations in South Africa. An early example was a survey among 636 pregnant women attending antenatal clinics in Cape Town and two other representative towns in the Western Cape Province, at a time when FAS had not yet come to attention as a public health problem [63]. Participants were predominantly of SAC ancestry (86%), with the remainder being of BSA ancestry. Of all study participants, 43% reported current drinking and 24% reported 5+ binge-drinking [63]. At each town, over 20% of pregnant women reported 5+ binge drinking, and over 5% reported more than 10 drinks per occasion, with no significant difference between sites.

More recently in metropolitan Cape Town, Petersen-Williams *et al* [64] reported prevalence rates from a survey of alcohol and other drug use among over 5000 pregnant women attending antenatal clinics. They found that 36.9% of women self-reported as current drinkers, but further details of drinking patterns and demographic characteristics were not available.

In a survey of nearly 1500 pregnant women attending primary care antenatal clinics in one district of Mpumalanga province, Louw *et al* [65] found much lower drinking rates: 6.6% were current drinkers and 1% (15.1% of drinkers) drank 5+ drinks per occasion.

A study of 1201 pregnant women with HIV in Kwazulu-Natal clinics found that 18% were current drinkers and 12% were 3+ drinkers [66]. Factors associated with drinking were urban or peri-urban residence, higher SES and greater social engagement.

In a prospective study of 580 HIV-positive, mainly BSA, pregnant women entering antenatal care in Cape Town, Brittain *et al* [67], 40% reported alcohol use during the 12 months prior to pregnancy. Alcohol use was characterised by binge drinking, with 65% beingg considered risky drinkers. Among risky drinkers, 70% subsequently reported reduced levels of consumption during pregnancy. The authors concluded that the alcohol use trajectories highlight an urgent need for an increased focus on screening and intervention at primary care level.

There is little information on temporal trends regarding in-pregnancy drinking, either in South African or other African countries. In the aforementioned national study [49], the authors reported an increase in past month alcohol consumption among pregnant South African women from 7.0% in a previous survey to 12.9% in 2005, although there were differences in study design. In contrast a recent study in Tanzania [68] found that, among 34,090 births at a medical centre between 2000 and 2010, the proportion of women reporting alcohol consumption during pregnancy decreased from 49.5 to 21.5%.

In summary, limited data is available on in-pregnancy drinking in South Africa. At a national level the prevalence of drinking appears to be significantly lower in pregnant women than other women. However, much higher levels of in-pregnancy drinking may occur in some sub-groups of the population defined by province of residence (Western Cape and Northern Cape), population group (SAC), or HIV positive status.

1.4 FETAL ALCOHOL SYNDROME AND FETAL ALCOHOL SPECTRUM DISORDER

1.4.1 FAS as a congenital disorder

The risks of prenatal exposure to alcohol were known in ancient times. For example the harmful effects of alcohol are suggested in the Old Testament of the bible: "Behold, though shalt conceive, and bear a son: and now drink no wine or strong drink" (Judges 13:7). Yet it is only recently that the clinical entity of fetal alcohol syndrome has been described, perhaps because the diagnosis relies on relatively subtle features. Lemoine *et al* (1968) [69] described congenital anomalies in a sizable cohort of children who were prenatally exposed to alcohol. The descriptions that firmly established the diagnosis of FAS are those of Jones and co-authors in 1973.

Jones *et al* [70] described a pattern of findings in a case series of 8 children born to alcoholic mothers. All cases had prenatal and postnatal deficiency of growth in both weight and length/height that did not improve with nutritional supplementation, microcephaly (head circumference < 3rd centile) and/or neurodevelopmental delay, and a pattern of minor dysmorphic features - in particular they noted small palpebral fissures (PFL, being the width of the eyes between medial and lateral canthi) and a small midface region. Shortly afterward Jones and Smith [71] described further cases with similar features and microphthalmia, malformations of the brain and other organs, and they named the condition fetal alcohol syndrome (FAS).

FAS thus refers to a pattern of facial dysmorphology, growth deficiency, as well as neurological and/or neurodevelopmental deficits that is specific to the effects of maternal alcohol use on the developing fetus.

Jones *et al* [70] were prescient in noting that their cases were associated with maternal alcoholism and were severe phenotypes, but that milder cases were also to be anticipated, because variability is common in teratogenic disorders. More recently FAS has been considered to be

the most severe end of a range of adverse clinical effects of prenatal exposure to alcohol [72].

The current umbrella term used to describe the full range of effects of prenatal alcohol exposure is fetal alcohol spectrum disorder (FASD) [73,74]. Additional conditions that are now included under the FASD umbrella are: partial FAS (PFAS) for cases with some of the syndromic features of FAS, alcohol related neurodevelopmental disorder (ARND) for cases with neurobehavioural effects but few syndromic features, and alcohol related birth defects (ARBD) for specific major birth defects due to alcohol exposure.

The focus of this thesis is predominantly on FAS, although, where relevant, specific reference is made to FASD, or to partial FAS, or to P/FAS when referring to cases that include both FAS and partial FAS.

1.4.2 The embryological and teratogenic basis for FAS/FASD

Although it is clear that maternal alcohol use in pregnancy is the primary risk factor for FAS/FASD, understanding the embryological and teratogenic basis for this is important in understanding why individuals and populations may be at increased risk. As is the case with most teratogens, the embryological basis of FASD is based largely on animal studies. These involve assessing morphological or neurological changes compared to controls, in fetuses exposed to different doses of alcohol at different times in gestation. While there are limitations in animal studies that make it impossible to extrapolate directly to humans [75], the findings can be used to corroborate the more indirect evidence in humans [76].

The teratogenic effect of alcohol can be described with reference to the six basic principles of teratogenesis laid out by Wilson [77], which remain relevant today. These are:

1. Susceptibility varies with developmental stage at time of exposure

2. A teratogen is toxic because of its specific effects on embryological development

3. Teratogens have four possible effects: miscarriage, growth retardation, malformations, and functional effects especially on neurodevelopment

4. There is a dose-response relationship

5. It is important to consider factors that influence access of teratogen to embryo

6. Susceptibility varies between individuals

Developmental stage*:* The embryonic period, during which the organs are formed, is the period in pregnancy which is most sensitive to teratogens, including alcohol. In humans, this extends from weeks 3-8 post-conception (weeks 5-10 after the first day of the last menstrual period, which is the pertinent clinical landmark). For practical purposes, many organs are susceptible to teratogenic exposure throughout the first trimester of pregnancy. It should however be noted that some organs, especially the developing brain, remain vulnerable to teratogenic effects throughout gestation.

Given that a woman is unlikely to recognise that she is pregnant before at least 6 weeks gestation, and sometimes not until later in pregnancy, significant embryonic exposure to alcohol can occur in any women who drinks and is sexually active while not using effective contraception, even if she stops drinking when she recognises her pregnancy. Evidence from clinical studies suggest that exposures in early gestation appear to be particularly important [78]. This is corroborated by animal studies [76].

Specific effects of alcohol*:* Major malformations (such as alcohol-related birth defects) relate to first trimester exposure, and the minor malformations that are the hallmark of FAS result from exposure within the first half of pregnancy [79]. Less regular exposure in this period may lead to partial FAS rather than FAS. The predominant target organ of alcohol is the developing brain, and since this remains vulnerable throughout gestation, ARND without dysmorphic features may result from later exposure in pregnancy, or exposure that is insufficient to cause morphological features of P/FAS. A wide range of abnormalities of brain structure or function can be detected on

neuroimaging modalities in prenatally alcohol exposed subjects with or without dysmorphic features of FAS [80].

***Four possible effects**:* Prenatal alcohol exposure can be associated with all four possible effects of prenatal exposure. A review by Bailey and Sokol [81] concluded that heavy prenatal alcohol use is associated with miscarriage, stillbirth and preterm delivery. Growth retardation, malformations and neurodevelopmental functional effects are sufficiently consistent that they are used in the diagnostic criteria for various subsets of FASD.

Dose response relationship: Animal studies have shown that the maternal blood alcohol concentration (BAC) appears to be important in development of dysmorphic features and microcephaly [78,82]. The strong epidemiological evidence that regular binge-drinking is a particularly high risk pattern for development of FASD [83,84], is consistent with evidence for BAC being crucial.

The current concept is that there is a threshold concentration level above which alcohol causes developmental toxicity, and that the duration for which alcohol is above this level is important in determining the severity of effect [85]. It should be noted that there is wide variation between women in the peak BAC and the time above any particular threshold BAC level, even if they ingest a similar amount of alcohol for their body size. It is therefore perhaps not surprising that clinical studies find that even a moderate amount of alcohol intake appear to carry some risk of adverse neurodevelopmental outcome [86].

***Factors influencing access of alcohol to the embryo/fetus**:* Alcohol readily crosses the placenta and the maternal BAC therefore equilibrates rapidly with the fetal BAC [85]. In addition to amount of alcohol consumed in a time period, a number of other factors influence maternal and fetal BAC. These include the woman's lean body mass (which determines the volume of distribution of alcohol), and whether the person takes food with alcohol (since this affects absorption).

***Susceptibility varies between individuals**:* Individuals vary in how rapidly they metabolise alcohol. Alcohol dehydrogenase (ALD) is the enzyme primarily responsible for alcohol metabolism. Several

ALD isoenzymes exist, with different pharmacokinetic properties. These are an important determinant of individual variation in alcohol metabolism. ALD variants in both the mother and the fetus may be important. Lewis *et al* [87] found that, in women drinking mild-moderate amounts of alcohol, worse neurodevelopment in offspring was associated with particular genetic variants in the alcohol metabolising enzymes, and that variants in both the mother and child may be relevant. In South African women, a study by Viljoen *et al* [88] found that a specific ALD polymorphism was less common in FAS children or their mothers than in controls.

It remains unclear whether alcohol exerts its toxicity only by a direct effect on the fetus, or whether other co-factors may provide the pharmacodynamic mechanisms by which alcohol causes FASD. Many possible co-factors/mediators have been investigated e.g. retinoids, oxidative stress due to free radicals, neurotransmitters such as glutamate [89] or broader nutritional state [90]. In this regard, May *et al* [91] found that a majority of women in a low SES South African community with a high prevalence of FASD had inadequate intake of multiple micronutrients, and that lower intake correlated significantly with heavy drinking. Such mechanisms would provide another possible source of individual variation, but to date no definitive mechanisms have been definitively identified.

In part because of individual variation, no threshold level of safe alcohol use in pregnancy can be defined.

Summary and clinical implications*:* Only a minority of alcohol-exposed pregnancies result in a diagnosable FASD, which may arise because BAC exceeds a threshold level for a sufficient period of time, and during a particularly vulnerable period of development, in a person who may be rendered vulnerable by a variety of additional personal or environmental risk factors. A combination of these factors may also determine whether the FASD is FAS, partial FAS, ARBD or ARND. It should also be recognised that other factors may more indirectly affect risk of FAS, for example the maternal health and nutritional state, and these need to be better defined.

Given the centrality of BAC, especially in early pregnancy but throughout pregnancy, the following points emerge:

- Rates of FASD are likely to depend on women's drinking, with both the quantity and pattern of drinking in pregnancy being important, and with rates of binge drinking and regularity of binge drinking being especially important
- Dysmorphic features of P/FAS reflect effects of alcohol in the first half and especially the first trimester of pregnancy
- Drinking before pregnancy recognition is important, and therefore so is a woman's drinking pattern throughout the reproductive age-range, if she is sexually active and not using effective contraception
- Individual variation in BAC is also influenced by factors other than amount of alcohol consumed in a session. These factors include maternal body size and particular variants in alcohol dehydrogenase
- At a population level, the proportions of syndromic and non-syndromic cases will vary with the common drinking patterns in the population.

1.5 KEY FEATURES OF A FAS DIAGNOSIS

The initial description of FAS was based on a 'gestalt' comprising: generalized growth retardation; a pattern of minor, often subtle dysmorphic features; and neurological, developmental and behavioural aberrations, in conjunction with a history of heavy alcohol use. Over time the assessment of each aspect has been refined, and various clinical classification systems established. Despite extensive attempts to establish biomarkers for the diagnosis of FAS, no reliable biomarkers have been found, and it remains a clinical diagnosis.

1.5.1 Growth

Heavy alcohol use has been associated with low birth weight, small size for gestational age and preterm birth: a meta-analysis of 36 studies found that consumption of >1-1.5 drinks per day led to 'monotonically increasing risk' of the above-mentioned adverse outcomes [92]. Even in the absence of intrauterine growth retardation, postnatal growth may be affected with the result that both weight and height are reduced. The affected child appears slender or even malnourished, despite an adequate diet [93]. At adolescence the picture may change, with weight gain especially in girls [83,94].

1.5.2 Dysmorphic features

Following the initial descriptions of FAS, further refinement of the dysmorphic features included the recognition that FAS is associated with dysmorphism of the upper lip area. In particular there is smoothing of the philtral ridges that extend from the nasal septum to the upper lip, and narrowing of the upper vermilion border with loss of the 'cupids bow' appearance [93].

Astley and Clarren [95] showed that a combination of three facial features (PFL, philtrum and vermilion border of the upper lip) were extremely sensitive and specific for the diagnosis of FAS. These features are considered to be the most diagnostically specific of all

FAS findings, and are often described as the primary dysmorphic features of FAS (Figure 3).

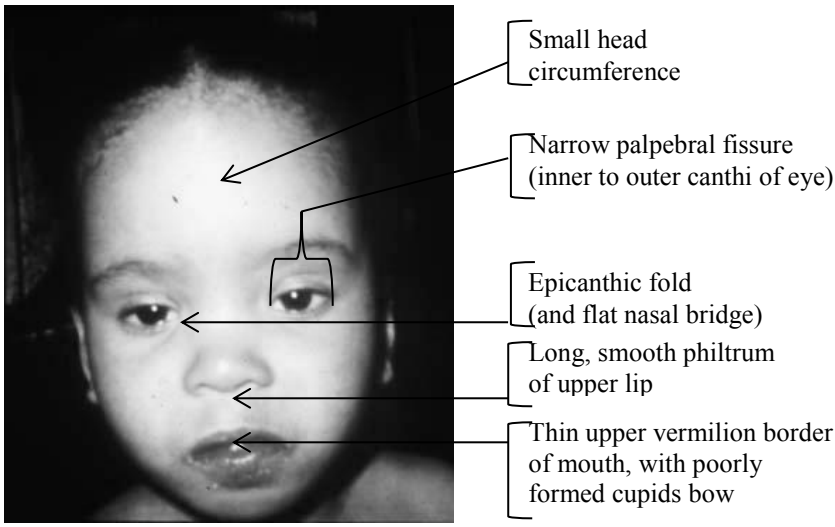
A difficulty with all three of the primary diagnostic features is that they are 'minor anomalies'. As is the case with most minor anomalies, each can be found in a proportion of normal individuals [93], and the combination of features is essential to diagnosis.

A range of other minor anomalies of the face and limbs have been described (Table 3) [74,93,96]. These are generally considered to be less diagnostically useful because they are either less sensitive or less specific than the primary features.

Further facial anomalies include: drooping (ptosis) of one or both eyelids, strabismus, flat nasal bridge and flattened midface, epicanthic folds of the eyes, anteverted nostrils, and a 'railroad track' appearance of the ear due to a prominent root of the helix.

Limb anomalies may include: unusual palmar creases (for example a 'hockey-stick' appearance of the distal transverse palmar crease), mild camptodactyly (incomplete extensions) of the fingers, clinodactyly with curving of a finger towards the middle finger, hypoplastic fingernails and shortened fifth fingers, as well as incomplete supination of the forearm due to radio-ulnar synostosis.

Figure 3: Facial features of FAS



The number of minor anomalies may be quantified as a 'dysmorphology score'. This is a useful adjunct to the primary dysmorphic features, with a high dysmorphology score confirming the likelihood of FAS. While most classification systems rely on the three primary dysmorphic features, at least one has given the dysmorphology score a more central role in diagnosis [97].

Major structural birth defects occur with increased frequency in FAS, but have no specificity for the diagnosis. These include congenital heart defects, cleft lip and palate, abnormalities of the urinary tract and genitalia, and spina bifida, which occur 5-60 times more often than in the general population [93]. In addition, further functional deficits may occur such as sensorineural or conductive hearing loss.

May *et al* [98] compared dysmorphic features among FAS cases and controls in three populations – native American (Northern Plains Indians), South African Coloured and Italian. They found that the dysmorphology associated with FAS varied across populations but that a combination of five dysmorphic features were consistently associated with FAS. These features were small palpebral fissures, narrow upper vermilion border of the upper lip, smooth philtrum of the upper lip, flat nasal bridge and fifth finger clinodactyly.

The minor dysmorphic features are considered to represent malformations that originate in the first half of pregnancy, and are not greatly impacted on by further influences at least until puberty. A multivariate analysis has demonstrated a strong associated between prenatal alcohol use and a number of the dysmorphic features of FAS [99].

After puberty, the face of a child with FAS often looks 'coarse' as a result of lengthening of the nose and enlargement of the chin, making the characteristic dysmorphic features more difficult to recognise [83].

Table 3: Dysmorphic features associated with FAS

Growth parameters	Height <10th centile
	Mass <10th centile
	Occipitofrontal circumference <10th centile
Facial features	Palpebral fissure length <10th centile
	Midface hypoplasia
	'Railroad track' ears
	Strabismus
	Ptosis
	Epicanthic folds
	Flat nasal bridge
	Anteverted nostrils
	Long philtrum
	Smooth philtrum
	Thin vermilion border of upper lip
	Prognathism
	Hirsutism
Arms/hands	Decreased supination of elbow
	Clinodactyly of 5th fingers (curve medially towards midline)
	Camptodactyly (clenching of one or more fingers - usually slight)
	Hypoplastic fingernails
	'Hockey stick' palmar creases
Organ systems	Congenital heart defect
	Other organ system malformations

Adapted from Hoyme *et al*, 2005[74]

1.5.3 Neurodevelopmental and behavioural

Despite the range of effects of alcohol on fetal development, the most important and primary effect is on brain development [90]. In addition, longitudinal studies have shown the neurodevelopmental effects to be the most permanently recognizable aspect of FASD.

Streissguth *et al* [83] studied a large cohort of children prenatally exposed to different amounts of alcohol. They found that by 14 years of age only those exposed to the highest doses of alcohol had the growth and dysmorphic features consistent with a diagnosis of FAS, whereas much broader dose-dependent effects were found on

neurobehavioural function. There were particular effects on attention, speed of information processing and learning problems especially for arithmetic.

Furthermore, Streissguth *et al* [100] in an earlier analysis of the same cohort, found a dose-dependent decrement of intellectual ability, with exposure to 1 ounce of absolute alcohol a day being related to a decrease in nearly five full-scale intelligence quotient (IQ) points. Neurodevelopmental effects are thus not restricted to those with syndromic features of FAS, and the results suggest that cognitive effects of prenatal alcohol exposure may be relatively common. This contention is supported by recent data of Mattson *et al* [101] which suggest that 70% of children prenatally exposed to heavy drinking are neurobehaviourally affected.

Coles *et al* [102] assessed a cohort of predominantly African-American children from low SES background. They compared children of mothers who drank throughout pregnancy, to those who stopped in pregnancy, to non-drinking controls. By school age, children of ongoing drinkers had smaller head circumferences and more severe, consistent and broad-ranging cognitive effects. Both alcohol groups were deficient in early mathematical and reading skills.

Studies of behaviour in the same cohort found that children exposed throughout pregnancy had deficits in the ability to sustain attention and were more often described by teachers as showing attentional and behavioural problems [103]. However, most of these findings weakened when the analysis was controlled for current drinking, indicating a strong effect on behaviour of the postnatal environment.

Howell *et al* [104] conducted a follow-up study of the same cohort in adolescence. They compared prenatally alcohol-exposed individuals with and without features of FAS to controls. In this economically deprived group they found that average IQ was relatively low in all groups but lower in those with FAS than either of the other groups.

Mattson and Riley [105] found the spectrum of cognitive and behavioral abnormalities seen in individuals exposed prenatally to alcohol to be broad. It included decreased IQ, hyperactivity, behavioral and adaptive difficulties, and deficits in motor function, attention, verbal language, executive function, and visuo-spatial skills.

Average IQ is most commonly in the borderline or below average range. Although some studies have found alcohol exposed children with and without FAS to have comparable neurocognitive problems [106], the preponderance of evidence suggests an average IQ of approximately 70 for children with FAS and approximately 80 for non-syndromic children with heavy prenatal alcohol exposure [101].

More recent evidence on cognitive function is summarised by Kodituwakku [107] and Mattson *et al* [101]. FASD is associated with a generalised decrease in cognitive function, with particular difficulty being experienced with more complex tasks in any given cognitive domain. There is evidence of particular involvement of working memory and executive function (planning, judgement and complex problem solving) [108]. These features are not specific to FASD, and the tests of executive function again show a discrepancy between performance of simpler and more complex tasks [107]. Similarly, a study of South African school entry children who were generally of low SES and SAC ethnicity found that children with FAS were markedly deficient only in higher-order cognitive-motor competencies [109].

Coles *et al* [110] described difficulties in paying attention that are similar in appearance but are not identical to typical attention deficit hyperactivity disorder. Mattson *et al* [101] further delineated the overlaps and differences between FASD and attention deficit hyperactivity disorder (ADHD), and have subsequently assessed links to adaptive functioning (the ability to modulate behaviour to a changing environment). Deficits in adaptive functioning have been consistently detected in the FASD population, manifested for example by poor communication and socialisation skills [111]. Given that apparent ADHD is often part of the profile of children with prenatal alcohol exposure, Ware *et al* [112] studied the effects of prenatal alcohol exposure and ADHD on adaptive functioning. They found that both prenatal alcohol exposure and ADHD reduced adaptive functioning, with a combination of the two being most deleterious.

In recent years some success has been achieved in using a neuropsychological profile to identify developmental problems secondary to the prenatal alcohol exposure. Studies using patients from the USA and South Africa found that a composite of 22 carefully selected neuropsychological variables (drawn from a set of 547 possible variables) were reasonably accurate at distinguishing

children with heavy prenatal alcohol exposure, with or without FAS, from controls [113]. A follow-up study found that similar variables were quite accurate at distinguishing children with heavy prenatal alcohol exposure from control children and children with ADHD [114].

Potential secondary disabilities include a wide range of problems, including: mental health issues, disrupted school experience, trouble with the law, alcohol and drug problems, problems with employment, or inability to live independently. These are reported to be very common in adolescents and adults with FASD [115]. This has not been confirmed in all settings, for example Howell *et al* [104], found no particular school conduct problems to be associated with prenatal alcohol exposure.

The studies of Coles [102] and Adnams [109] in particularly were conducted in low SES communities in the USA and South Africa respectively. In both cases the control groups also had relatively compromised developmental parameters. The effects of prenatal alcohol exposure cannot be considered separately from the broader context affecting the child. It is well known that poverty adversely affects child development [116] and that a multiplicity of factors contribute to this [117].

In a South African setting with a high prevalence of FASD, May *et al* [118] conducted a multivariate analysis of 19 risk factors for poor child development among school entrants. They found that the effects of prenatal alcohol exposure appeared to be overpowered by socio-economic and maternal physical factors, and concluded that these factors make a significant enabling or disabling contribution to child functioning in FASD.

As a result of the improved specificity of neuropsychological findings, the recently published DSM-V created a new category to encompass the neurodevelopmental effects of prenatal alcohol exposure: neurobehavioural disorder associated with prenatal alcohol exposure (ND-PAE) [119]. This identifies three core areas of deficits: neurocognitive, self-regulation, and adaptive functioning impairments. It requires that, in addition to deficits in each of the three domains, there should be confirmation of drinking which is more than 'light' (i.e. ≥14 drinks per month, or 3+ drinks per occasion). The definition also notes that interactions may occur with difficult childhood circumstances (which appear to compound the

effects of PAE), and with other drugs (which affect behavioural regulation more than neurocognitive status). Although not part of the definition, ND-PAE is commonly associated with secondary mental health disorders and with personality disorders. Further clinical research is required to determine whether this new clarifying term and classification will lessen reliance on dysmorphic features, and thereby broaden access to accurate diagnosis.

There is compelling evidence for neuroplasticity in early brain development [120]. A systematic review of interventions for FASD by Reid *et al* [121] found growing evidence for interventions that improve outcomes for early to middle childhood, although there is little research outside of this developmental period. In South African school children, a language and literacy intervention showed improvement in specific aspects of language and literacy [122].

Paley and O'Connor [123] outline a wide range of interventions for FASD, which range from early childhood interventions e.g. targeting parenting skills, to school educational support, to case management for secondary disabilities, but noted that existing interventions were generally not specific to FASD. In view of the value of early intervention, the need for early diagnosis of FASD has been endorsed by organisations such as the American Academy of Pediatrics [124].

1.5.4 Assessing alcohol use in pregnancy

In general, self-reported use is the method of choice for determining whether alcohol was consumed in pregnancy. A range of other approaches is available, such as the use of biomarkers, but these are of value only for prospective studies and have imperfect sensitivity and specificity [125]. This means that there is no 'gold standard' method that is clearly better than self-reported use.

Self-reported use on the other hand has been shown to be valid if correctly obtained [126]. Questionnaires should be guided by an appropriately skilled interviewer rather than be self-completed, especially in the context of binge drinking, as this has been found to better predict future drinking behaviour [127]. The accuracy of information obtained relates to the particulars of the assessment situation, the respondent and the measurement instrument [128,129]: the assessment situation should be private and the client assured of

confidentiality, the interviewee should be alcohol-free when interviewed, and the measurement instrument should use objective questions and provide for memory aids to be used.

In general a high degree of correlation has been found when comparing self-report to report by a significant other, or other close friend or relative [130].

Research-based questionnaires regarding alcohol use most commonly obtain direct information about alcohol use in a time interval. This may be in the form of a quantity and frequency of use (assesses average daily consumption and average frequency of use), or a daily drinking assessment for each day in the interval [126]. Both of these approaches gather information about numbers of standard drinks consumed.

An alternative approach is the use of a screening tool to assess the level of drinking indirectly, by enquiring after symptoms suggesting dependence, or drinking levels suggesting hazardous use. A range of such tools is available, for example the AUDIT [131], AUDIT-C [132,133], CAGE. Some of these tools, like the T-ACE, TWEAK have been specifically validated in pregnancy [134]. Although used in research, these methods were developed primarily for rapid screening in a clinical environment.

In the context of FAS assessment, information about alcohol use in pregnancy is often obtained retrospectively. Methods such as the alcohol timeline follow-back (TLFB) approach have been developed for retrospective estimation of daily drinking for a specified time period [135]. Memory aids used to enhance recall include use of key events to serve as prompts. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) considers this a relatively accurate portrayal of the magnitude, pattern and variability of past drinking (https://pubs.niaaa.nih.gov/publications/assessingalcohol/InstrumentPDFs/13_TLFB.pdf).

The TLFB method has been validated for use in several languages, and in different countries [136,137]. A similar approach has been adapted specifically for the South African situation [138]. It assesses daily drinking over the past week, and then for one week intervals prior to pregnancy and during each pregnancy trimester. This has been used extensively in South Africa, for example by Viljoen *et al* [139] and May *et al* [140].

Concerns have been raised about the accuracy of retrospective assessment of alcohol use, in view of the possibility of recall and social desirability bias, and of memory issues related to heavy or binge drinking, and related to the fact that interviews may occur several years after the index pregnancy. In a USA-based study, levels of alcohol use reported retrospectively were substantially higher than reported during pregnancy [141]. On the basis that drinking in pregnancy is stigmatised and that women are expected to under-report it, the interpretation was that retrospective report may be more accurate than a history taken in the antenatal period. More recently, it has been found that even up to 14 years post-partum, retrospective report detects higher rates of drinking than antenatal report [142].

1.5.5 Classification of FASD

An accurate diagnosis of FASD made as early in life as possible is important for several reasons. It facilitates intervention for the child, and allows one to address maternal drinking both for the sake of her health and to prevent recurrence in future children.

To improve diagnosis of the FASD, the US Institute of Medicine (IOM) [72] developed a standardised classification system. This included the following four diagnostic categories: FAS (with or with confirmed fetal alcohol exposure), partial FAS (with confirmed exposure), ARND (with confirmed exposure), and ARBD (with confirmed exposure).

While this classification system was an important milestone, limitations were identified by various authors with different professional backgrounds, working in different contexts, who adapted the guidelines with different purposes in mind. Currently, several classification systems exist, the best known of which are the FASD 4-Digit diagnostic code [143], the Centers for Disease Control Guidelines for FAS referral and diagnosis [144], the Canadian FASD guidelines [145,146], and the revisions of the IOM guidelines proposed by Hoyme *et al* [74,147].

The various diagnostic guidelines differ on a range of parameters. These include: the number of sentinel facial features required for a diagnosis; the inclusion of growth deficits as a diagnostic criterion; the neurodevelopmental assessment process and criteria; and the

approaches and measures used to confirm prenatal alcohol exposure. As a result there is imperfect agreement between the diagnostic systems, although this is better for specific categories such as FAS which are more clinically characteristic [97,148].

Researchers conducting epidemiological surveys of FAS in South Africa have historically used the IOM classification (for example May *et al*, 2000 [167]), and subsequently the Hoyme adaptation [74] which is included as Table 4. The latter was developed by a group of US and South African researchers, in part with the South Africa setting in mind. They have been used extensively and internationally in studies of FAS, for example in Italy [149], Croatia [150], the USA [151] and in South Africa [152].

In children with neurodevelopmental problems, and a history of maternal alcohol consumption but without characteristic dysmorphism, ARND is diagnosed. The non-specific nature of ARND and the milder end of the FASD spectrum creates difficulty for both diagnosis and screening. A large recent study in South Africa found ARND to be a less common than FAS but nevertheless common: ARND was diagnosed of 3.1-4.7% of all children in a community with a very high total FASD rate of 13.6-20.9% [152]. For this reason, the studies in this thesis focus on FAS especially, as well as partial FAS.

Table 4: Proposed Clarification of the 1996 IOM Criteria for Diagnosis of FASD

TABLE 2. Proposed Clarification of the 1996 IOM Criteria for Diagnosis of FASD

I. FAS With Confirmed Maternal Alcohol Exposure (requires all features A–D)
- A. Confirmed maternal alcohol exposure
- B. Evidence of a characteristic pattern of minor facial anomalies, including ≥2 of the following
  1. Short palpebral fissures (≤10th percentile)
  2. Thin vermilion border of the upper lip (score 4 or 5 with the lip/philtrum guide)
  3. Smooth philtrum (score 4 or 5 with the lip/philtrum guide)
- C. Evidence of prenatal and/or postnatal growth retardation
  1. Height or weight ≤10th percentile, corrected for racial norms, if possible
- D. Evidence of deficient brain growth or abnormal morphogenesis, including ≥1 of the following
  1. Structural brain abnormalities
  2. Head circumference ≤10th percentile

II. FAS Without Confirmed Maternal Alcohol Exposure
- IB, IC, and ID, as above

III. Partial FAS With Confirmed Maternal Alcohol Exposure (requires all features, A–C)
- A. Confirmed maternal alcohol exposure
- B. Evidence of a characteristic pattern of minor facial anomalies, including ≥2 of the following
  1. Short palpebral fissures (≤10th percentile)
  2. Thin vermilion border of the upper lip (score 4 or 5 with the lip/philtrum guide)
  3. Smooth philtrum (score 4 or 5 with the lip/philtrum guide)
- C. One of the following other characteristics
  1. Evidence of prenatal and/or postnatal growth retardation
     a. Height or weight ≤10th percentile corrected for racial norms, if possible
  2. Evidence of deficient brain growth or abnormal morphogenesis, including ≥1 of the following
     a. Structural brain abnormalities
     b. Head circumference ≤10th percentile
  3. Evidence of a complex pattern of behavioral or cognitive abnormalities inconsistent with developmental level that cannot be explained by genetic predisposition, family background, or environment alone
     a. This pattern includes marked impairment in the performance of complex tasks (complex problem solving, planning, judgment, abstraction, metacognition, and arithmetic tasks); higher-level receptive and expressive language deficits; and disordered behavior (difficulties in personal manner, emotional lability, motor dysfunction, poor academic performance, and deficient social interaction)

IV. Partial FAS Without Confirmed Maternal Alcohol Exposure
- IIIB and IIIC, as above

V. ARBD (requires all features, A–C)
- A. Confirmed maternal alcohol exposure
- B. Evidence of a characteristic pattern of minor facial anomalies, including ≥2 of the following
  1. Short palpebral fissures (≤10th percentile)
  2. Thin vermilion border of the upper lip (score 4 or 5 with the lip/philtrum guide)
  3. Smooth philtrum (score 4 or 5 with the lip/philtrum guide)
- C. Congenital structural defects in ≥1 of the following categories, including malformations and dysplasias (if the patient displays minor anomalies only, ≥2 must be present): *cardiac*: atrial septal defects, aberrant great vessels, ventricular septal defects, conotruncal heart defects; *skeletal*: radioulnar synostosis, vertebral segmentation defects, large joint contractures, scoliosis; *renal*: aplastic/hypoplastic/dysplastic kidneys, "horseshoe" kidneys/ureteral duplications; *eyes*: strabismus, ptosis, retinal vascular anomalies, optic nerve hypoplasia; *ears*: conductive hearing loss, neurosensory hearing loss; *minor anomalies*: hypoplastic nails, short fifth digits, clinodactyly of fifth fingers, pectus carinatum/excavatum, camptodactyly, "hockey stick" palmar creases, refractive errors, "railroad track" ears

VI. ARND (requires both A and B)
- A. Confirmed maternal alcohol exposure
- B. At least 1 of the following
  1. Evidence of deficient brain growth or abnormal morphogenesis, including ≥1 of the following
     - a. Structural brain abnormalities
     - b. Head circumference ≤10th percentile
  2. Evidence of a complex pattern of behavioral or cognitive abnormalities inconsistent with developmental level that cannot be explained by genetic predisposition, family background, or environment alone.
     - a. This pattern includes marked impairment in the performance of complex tasks (complex problem solving, planning, judgment, abstraction, metacognition, and arithmetic tasks); higher-level receptive and expressive language deficits; and disordered behavior (difficulties in personal manner, emotional lability, motor dysfunction, poor academic performance, and deficient social interaction)

In the proposed diagnostic criteria, the following considerations apply. Each of the categories assumes that genetic and medical assessment has ruled out a phenocopy, including other genetic and malformation syndromes. Confirmed maternal alcohol exposure is defined as a pattern of excessive intake characterized by substantial regular intake or heavy episodic drinking. Evidence of this pattern may include frequent episodes of intoxication, development of tolerance or withdrawal, social problems related to drinking, legal problems related to drinking, engaging in physically hazardous behavior while drinking, or alcohol-related medical problems such as hepatic disease. Confirmation may be from maternal interview or reliable collateral sources.

ARBD and ARND refer to clinical conditions in which there must be a history of maternal alcohol exposure, and in which clinical and/or animal research must link maternal alcohol ingestion to the observed outcome. ARBD encompasses children with major and/or minor structural anomalies who display normal growth and intellectual development. ARND comprises a specific pattern of disordered behavior and development among children with normal growth and structural development.

(From Hoyme *et al*, 2005[74])

1.5.6 Practical identification and synthesis of a FAS diagnosis

Measuring the prevalence of FAS is a difficult undertaking. As has been described the diagnosis is made on a clinical basis and includes four different components: (1) anthropometric measurements (2) dysmorphic features, especially of the face (3) neurological, neurodevelopmental or behavioural abnormalities (4) history of maternal drinking in pregnancy. Of these only the first is easily obtained.

Assessment of the dysmorphic features requires expertise and experience, and is usually performed by a medical geneticist or paediatrician with specific dysmorphology interest. The PFL in particular must be carefully measured. This requires cooperation from the child and is difficult in infancy. Description of the upper lip is facilitated by comparison with a photographic Likert scale. The IOM classification lists a number of minor dysmorphic features, and these need to be assessed, using a checklist. If several are present they add to the certainty of diagnosis. Expert assessment of dysmorphism, together with a general and neurological assessment can be expected to take at least 10-15 minutes.

The dysmorphic features of FAS are less easy to assess accurately in infancy and become less characteristic after puberty [83]. Assessment of dysmorphism is thus most commonly performed in early to mid-childhood. Other difficulties that may arise include differences in the normal appearance between different families or populations. The average appearance of the nose and upper lip vary between populations. Specific Likert scales have been created for Caucasians [95], African-Americans [148], and recently for the SAC population [153].

Alternative methods have been assessed for assessing dysmorphological features especially facial feature measurement (e.g. 3D camera), but these cannot currently replace expert assessment. Difficulties in these approaches include the fact that features depend to some extent on an assessment of the 'gestalt'. In addition, there are a number of conditions with overlapping clinical features that need to be excluded clinically and if necessary by further testing. These

include: Williams syndrome, velocardiofacial syndrome, Dubowitz syndrome, Cornelia-de Lange syndrome and others [74].

A neurological assessment is conducted together with the dysmorphic assessment, but a full neurodevelopment assessment is also required unless the neurological assessment gives sufficient information to make a diagnosis of FAS. Currently, there is no accepted pathognomonic neurodevelopment profile for FAS, and assessment must cover a broad range of developmental domains, and be performed by a paediatrician or psychometrist with expertise in child development. Neurodevelopmental assessment is less accurate in infancy [154]. This assessment can take at least an hour.

The maternal interview is also a time-consuming process, at least in the research context, because it gathers data about a range of variables of interest (see methods section 3.2.1), and detailed retrospective data about alcohol use currently, and then before during and after pregnancy. It is essential that a trusting relationship is established in view of the sensitivity of questions around alcohol and drug use in pregnancy, and to ensure that information is as accurate as possible.

Even in the best hands diagnosis of FAS, and especially the less specific diagnoses in the FASD spectrum, remains imperfect. This is reflected by the existence of several sets of clinical diagnostic criteria. A comparison of the modified IOM criteria and the 4-digit code found that they yield overlapping but not identical diagnoses [148]. Even with current best practice, it is possible that some cases may be misclassified, although this proportion is likely to be small for FAS since it is the most clinically evident form of FASD. If the alcohol history is available it increases the certainty of the diagnosis. Given the range of components to the diagnosis, the diagnosis must be made cautiously except in the most obvious cases.

In light of the above discussion, it is not surprising that FASD is often not detected in routine healthcare. Little *et al* [155] found that, of 40 newborns born to heavy drinkers and with features of FAS, none were discharged with a diagnosis. Clarren *et al* [156] reported that a very low rate of prior diagnosis of FAS in school entry children studied, with only 1 of 7 cases of FAS being previously diagnosed. Stoler and Holmes [157] found significant under-detection of both maternal alcohol use and FAS, and concluded that there is a need for ongoing

education of health professionals regarding the importance of asking about prenatal alcohol exposure and the spectrum of fetal alcohol effects are needed for early diagnosis.

Jones [154] described the paradox of FASD being a difficult diagnosis to make early, but that there is a need for early recognition, for several reasons: early intervention to reduce the development of secondary disabilities and provision of necessary services for affected children, adequate therapy (possibly including drug therapy for associated behavioural abnormalities) and prevention of recurrence in future children. In the US it appears that detection of FAS has improved in recent times, but stigma around drinking in pregnancy results in non-syndromic FASD remaining an 'unseen disability' [123].

1.6 PREVALENCE OF FAS

1.6.1 Study methods to determine FAS prevalence

Given the potential significance of FAS and FASD as a public health problem, there is a need to determine prevalence as accurately as possible, on as wide a scale as possible, and to monitor the prevalence over time. Studies have tended to focus on FAS because it is better defined than other conditions in the FASD spectrum, but even so the difficulties extend beyond the time-consuming nature of individual assessments. This section will briefly outline approaches used in a developed country and assess their utility in a South African context.

In the USA FAS was recognised to be a potential public health problem in the 1970s, and three broad approaches have been used for generating data on the prevalence, each with advantages and disadvantages. May and Gossage [158] describe these as:

(1) Passive systems: the use of birth defect surveillance data, or studies using hospital records, birth certificates, registries and other data sources in which a FAS (or FASD) diagnosis may be recorded.

(2) Clinic-based studies: prospective studies which recruit women in antenatal clinics and follow them prospectively until childbirth, at which time the infant can be assessed for features of FAS.

(3) Active case ascertainment studies: cross-sectional or case control studies specifically designed to detect prevalence of FAS in a defined geographical area.

Passive systems in the USA initially focused on the newborn period or infancy [159]. An example is the US National Birth Defects Monitoring Program (BDMP), which samples a significant proportion of the US birth cohort for birth defect information reported in the hospital discharge diagnoses of newborns. As described above, the diagnosis of FAS is difficult in infancy, and methods were developed to use multiple data sources and extend further into infancy and childhood. Cordero *et al* [160] compared a multisource passive surveillance system covering data pertaining to the first year of life to data derived from a longitudinal research study, and found that the passive method detected only 38% of cases. Passive surveillance, even in countries with well-developed data systems, tend give much lower estimates than other methods.

In the USA, a more specific approach to surveillance for FAS became available in several states in the late 1990's, with the development of the US Fetal Alcohol Syndrome surveillance network. This added an active surveillance element which involved the use of a FAS case definition for surveillance, and development of rules for case detection. This was deployed to actively screening multiple sources of documentary information for cases of FAS. The aim was to capture information for at least the first 2 years of life [161], but ideally up to 8 years [159].

In the South African context, surveillance for CDs including FAS remains poorly developed. A national South Africa Birth Defects Registry exists but is under-resourced and relies on health professionals to complete a paper-based reporting form. Lebese *et al* [162] assessed the registry for CDs captured during a 9-year period from 2006 to 2014. They reported that, comparing all reported cases to the expected numbers [38], the registry data represent a >98% under-estimate for all CDs.

In the study by Lebese *et al* [162], only 73 cases of FAS were reported. As may be expected, FAS was much less commonly reported than birth defects more readily identified in the neonatal period. FAS was 11 times and 17 times less frequently reported than neural tube defects or Down syndrome, respectively. This is despite the fact that, as our data will show, FAS is more common that the above-mentioned conditions in large parts of the country. In a developing country setting, with rather under-developed surveillance systems, passive methods cannot be relied upon for accurate date.

Clinical-based studies have the strengths of prospective research design, the inclusion of controls, and the ability to gather maternal history data. Weaknesses include the potential to under- or over-estimate the prevalence of FAS. Antenatal clinics may be chosen because they are expected to be at increased risk, leading to overestimation of FAS prevalence. Underestimation may result from poor attendance of antenatal care by heavy drinkers, or because infancy is not the optimal time for FAS status to be assessed [93]. Longer prospective follow-up allows for more optimal assessment of FAS outcomes and assessment of exposure and outcome, but is much more costly and complex.

Comparison of prospective clinic-based studies has yielded important information regarding FAS prevalence. Abel [163] assessed prospective studies from a range of developed countries and found that the prevalence of FAS varied greatly between sites, and it occurred much more commonly in the USA than in Europe, despite higher overall female drinking rates in Europe, a fact which he dubbed the 'American paradox'. Abel juxtaposed this to the previously described but only obliquely related 'French paradox': France has high per capita alcohol consumption, and high rates of direct complications such as liver cirrhosis, but low rates of common disorders such as coronary heart disease. Research on the 'French paradox' has shown that regular light drinking protects against coronary heart disease, whereas the 'American paradox' has helped stimulate research on additional risk factors for FAS (see section 1.7).

The **active case ascertainment** method was initially applied in Native American reservations in the USA [164], and is suitable for estimating prevalence of FAS in relatively large populations in specific geographical areas such as schools, towns or districts.

Because the method is specifically tailored to determining prevalence of FAS, children can be recruited at an optimal age for FAS assessment (such as at school entry), and to ensure broad coverage of the population studied. This includes improved detection of high-risk subgroups e.g. by including schools for learners with special educational needs. Active-case ascertainment may therefore provide the most complete picture on prevalence of FAS, and associated population characteristics, in a particular population [165].

Disadvantages of the active case ascertainment approach include the fact that it is relatively costly and labour intensive, though less so than long-term prospective follow-up. It is also requires acceptance by the community, and the involvement of a wide range of organisations e.g. governments departments of education, social services, health. Because active case-ascertain studies tend to be targeted at areas which are believed to have high rates of risky alcohol use, they may lead to over-estimation of FAS prevalence in the population at large. A converse problem is that such studies are not designed to detect the full range of effects of maternal alcohol use on child development, and therefore underestimate the full range of FASD outcomes.

In considering appropriate methods to assess prevalence in South African circumstances, there are a number of practical considerations. A first priority was to generate practical information on prevalence of FAS across a range of South African environments. As such a method tailored to detecting FAS, rather than for researching prospective outcomes of maternal alcohol consumption, was more appropriate and cost-effective. It was also clear that in our context, it would not be possible to rely on the passive surveillance approach, given the severe limitations of such data in our environment for all CDs, but for FAS in particular. As such, we used primarily active case-ascertainment methods to determine FAS prevalence.

It should be noted that an alternative approach is to focus only on data for female drinking and alcohol exposure pregnancies. However, this does not directly describe FAS and related clinical outcomes. Given the wide range of factors that appear to determine whether alcohol use leads to the clinical outcome of FAS/FASD, it is inadequate to focus on drinking by reproductive age or pregnant women as a proxy for FAS, although this provides important complementary information.

1.6.2 Epidemiology of FAS internationally and in South Africa

As described above there are different methods of surveillance for FAS and FASD. Since ascertainment is difficult for non-syndromic cases, prevalence rates for FAS, and to some extent also partial FAS, are more often quoted. Published studies conducted in South Africa to date have been exclusively of the active case ascertainment type, and this section will be restricted to comparable studies.

Roozen *et al* [166] conducted a systematic review of FASD prevalence worldwide. Table 5 shows extracted results of studies that used active case-ascertainment methods and quoting rates of FAS in general populations, and in mid-childhood. Such studies are likely to provide the most accurate picture of FAS and partial FAS in a society, with two caveats. First, they are not necessarily nationally representative, and second they do not address the broader issue of non-syndromic neurodevelopmental effects.

The South African studies listed are those conducted prior to the publications presented in this document. Most were performed in the Cape Winelands district because of concerns that it was a particular high risk area. A landmark study funded by the NIH used active case-ascertainment methods among school entrants, and found a FAS prevalence of 40.5-46.4 per 1000 [167], considerably higher than documented elsewhere. A follow-up study in the same area raised concerns about a possible increasing prevalence of FAS [139], but this appeared stable on a third study.

A study sponsored by the US Centres for Disease Control (CDC) [168] and conducted in several areas of Johannesburg in the Gauteng Province, showed a prevalence of FAS considerably lower than in the Cape Winelands, and at the upper end of the range of studies in other countries.

Table 5: Prevalence of FAS and partial FAS from active case-ascertainment studies

Population	FAS prevalence (per 1000)	Partial FAS prevalence (per 1000)	Sample size	
USA				
Native Americans	2.4		22,963	May *et al*, 1983 [164]
	5,9		1,013	Burd *et al*, 1999[169]
County 1 County 2	4.9 5.2		1,630 2,110	Clarren *et al*, 2001[156]
	8.4	16.1	1,433	May *et al*, 2014 [151]
Australia				
	0.45		55,392	Elliott *et al,* 2008 [170]
	7.9	1.2	127	Fitzpatrick *et al*, 2015 [171]
Croatia				
	6.4	34.3	466	Petkovic and Barisic, 2010 [172]
	17.0	49.8	824	Petkovic and Barisic, 2013 [150]
Italy				
	7.4	31.1	543	May *et al*, 2006 [173]
	8.2	36.9		May *et al*, 2011[158]
South Africa				
Gauteng	19.3		830	CDC, 2003[168]
Cape Winelands	46.5		992	May *et al*, 2000 [167]
	74.2		863	Viljoen *et al*, 2005[139]
	67.2	22.0	818	May *et al*, 2007 [140]

(Adapted from Roozen *et al*, 2016 [166])

1.7 MATERNAL RISK FACTORS

1.7.1 Risk factors for an alcohol-exposed pregnancy (AEP)

Female drinking during the reproductive age range is a risk for AEP during the perinatal period, especially because a high proportion of pregnancies are unplanned and because there is often a significant gap between the onset of pregnancy and its recognition. Risk factors for peri-conceptional drinking have been studied extensively, as have risk factors for drinking at the time of interview during pregnancy, but the risk of ongoing drinking throughout pregnancy has been less extensively examined.

This brief summary, amplified in the next section on AEP in South Africa, highlights not only the wide range of individual risk factors for an AEP, but also the variety of types of risk factors. These include demographic and social variables, in-pregnancy or childhood exposure to abuse, as well as psychological states and personality traits.

Floyd *et al* [56] found that the risk factors for frequent drinking in the peri-conceptional period included being unmarried, a smoker, white non-Hispanic, 25 years of age or older, or being college educated. Haynes *et al* [174] found that risk factors for in-pregnancy drinking by 232 US women were older maternal age, white Non-Hispanic population group, recent physical abuse and to a lesser extent general health.

A study across eight US states [58] found that both drinking and binge drinking during pregnancy were predicted by pre-pregnancy binge drinking. Drinking and binge drinking during pregnancy also were more prevalent among women who were non-Hispanic whites, those who smoked during pregnancy, and whose pregnancy was unintended.

A review of 14 studies of drinking during pregnancy in nine countries, including one African country [175], found that women's pre-

pregnancy alcohol consumption, and exposure to abuse or violence were consistently associated with drinking during pregnancy. High SES was a less consistent predictor, whereas unemployment, marital status, and education level were rarely found to be predictive.

Maternal age is an important variable - in the USA women who become pregnant in their thirties and forties are more than twice as likely to drink during pregnancy than younger women [18].

In the Netherlands, Beijers *et al* [176] found that ongoing drinking in pregnancy was associated with particular personality traits, namely in those who scored high for openness to new experiences and low for conscientiousness. In addition, they found that stressful life events - including conflict with loved ones, crime-related and pregnancy-specific stress - were associated with ongoing drinking [176].

1.7.2 Risk factors for AEP in South Africa

Several South African studies have explored risk of AEP in South Africa. Morojele *et al* [177] studied two samples of pregnant women with very different demographic composition. The rural sample was in the Western Cape Province and predominantly from the SAC population group. The urban sample was in Gauteng province and predominantly from the BSA population group. Rural women (22%) were more likely than their urban counterparts (11%) to be at risk of an AEP. In multiple logistic regression analyses, significant predictors of risk in urban women were ethnicity, with white and SAC women at higher risk than BSA women, and current smoking. For the rural women, significant risk factors were current smoking and early onset of alcohol use. Significant protective factors were education, knowledge about FAS and parity.

O'Connor *et al* [178] studied 24 neighbourhoods in the Cape Flats outside Cape Town, South Africa. Among 619 pregnant women of BSA ethnicity drinking prior to pregnancy recognition was associated with being younger, single, better living conditions, smoking, longer gestation prior to pregnancy recognition, more sexual partners, and a higher incidence of intimate partner violence (IPV). Depressive symptoms tended to be higher among alcohol users.

Brittain *et al* [67] studied HIV positive women of predominantly BSA ancestry and found that alcohol use prior to pregnancy recognition was associated with single relationship status, experience of IPV, and lower levels of HIV-related stigma. Risky drinkers were more likely to report having experienced IPV and higher education levels than other drinkers. Factors independently associated with reducing consumption in pregnancy included: earlier gestation when entering antenatal care and report of a better patient-healthcare provider relationship.

1.7.3 Risk factors for FASD

I have outlined above the compelling evidence that heavy prenatal alcohol exposure results in an increased risk of effects on prenatal and postnatal growth, predictable dysmorphic features and/or adverse neurodevelopmental outcomes that comprise FASD. There is no threshold level of alcohol intake that is useful to completely exclude risk, or conversely to guarantee adverse outcome. In part this reflects the existence of other factors that modify risk. In the American context, it is considered that 10-15% of exposed pregnancies are later found to have diagnoses in the FASD spectrum [179] though this risk may vary according to drinking practices and other risk factors.

May and Gossage [180] give a useful overview of the range of risk factors have been described for development of FAS. They divide these factors into three groups: agent (alcohol) exposure, host characteristics, and environmental features. This categorization has been adopted in the table of factors associated with FAS (Table 6). In addition to the literature on risk factors for FAS data on risk factors for AEP, and alcohol use disorders more generally, have been included in Table 6 for comparative purposes.

FASD is an important 'harm' of female drinking, and can be conceptualised in a similar manner to alcohol-related harms more generally (see discussion above). As described previously, a pattern of regular binge drinking, especially in early pregnancy, but often extending throughout pregnancy is a particularly high risk pattern of drinking [78].

In addition to quantity and pattern of drinking, it is important to consider the underlying distal or higher level factors, and the

mechanisms by which they predispose to FAS. Low SES is one such high level factor, and its link with FAS may be mediated by multiple intermediate factors: social, such as the particular drinking culture; psychosocial, such as the stresses or psychological states associated with drinking; and biological such as nutrition-related factors linked to FAS.

It is important to understand whether the risk factor predisposes to risky drinking associated with high BAC or via an independent mechanism. Discordance for FAS status between dizygotic twins [181] suggests that maternal BAC is not a final common pathway, and that maternal and fetal genotype may play a role, or that intrauterine environment is a co-factor. For example, do small maternal size and poor nutrition, or smoking, primarily alter BAC, or do they increase vulnerability in other ways? At this state there is evidence for the effects of nutrition on volume of distribution and alcohol metabolism [182], but also for other possible pathogenic effects [89], though much remains unknown.

In the text below I briefly highlight some issues related to the causal network for FAS.

Risk factors which are concordant for FAS and for drinking are likely to indicate that alcohol use mediates the link between the risk factor and FAS, although it does not exclude additional mechanisms. In Table 6, these include: mother unmarried, stressed or depressed, or smokes cigarettes or other substances; partner or other family members drink.

Alcohol may both relieve and exacerbate stress [183]. Recent and previous stress are considered important associations with risky alcohol use, including binge drinking. A range of stressors have been shown to influence alcohol consumption, which Keyes *et al* [184] separate into four categories: general life stress, catastrophic stress, childhood maltreatment and minority stress.

Psychiatric comorbidities such as depression and generalised anxiety disorder have been associated with alcohol dependence, although the evidence appears less clear for binge drinking [185]. Not all psychological factors linked to heavy alcohol use have been extensively explored as risk factors for FAS: important examples

including early life trauma and abuse [186], post-traumatic stress disorder and intimate partner violence [18] This seems to have received limited attention in the FAS literature, though Kvigne *et al* [187] found that the odds of accidental and 'intentional' injury (which was not clearly defined) were respectively 3 and 6 times higher in children with FAS than controls.

More distal factors affecting drinking behaviour have been studied extensively. Ennet *et al* [188] assessed factors associated with risky use of alcohol by adolescents, using Bronfenbrenner's ecological systems theory of child socialisation and development, and found that risk factors existed at multiple levels: personal, relationships with family and peers, and broader context such as schools and media.

Social networks have been shown to be important determinants of drinking behaviour. Using the Framingham research cohort, Rosenquist *et al* [189] found that individual drinking patterns were associated with drinking habits of friends and relatives but not neighbours and co-workers, with the temporal relationships suggesting that the relationship may induce individual drinking patterns. Lorant and Nicaise [190] found that individuals more central to student social networks were more likely to binge-drink.

A person's perception of social norms is a determinant of drinking practice, and a study of university students found that many overestimated the level at which others drink, or approve of drinking [191].

Other risk factors for FAS appear to be less clearly associated with drinking. This raises the possibility of the link between the risk factor and FAS not being mediated by alcohol, although such an interpretation should be made cautiously. These factors include low SES, educational level, and perhaps also ethnic group affiliation.

Abel [192] noted that several risk factors for FAS were linked to socio-economic status, and commented that 'FAS is not an equal opportunity birth defect' because low SES is associated with a 10-fold increased risk of FAS. This is consistent with the broader link that has been made between poverty and alcohol-related harm [6].

Some risk factors may affect drinking, but also appear to have additional effects. For example, advancing maternal age is associated with greater likelihood of drinking in pregnancy [18], but evidence from a longitudinal cohort study indicates that it also predisposes to adverse childhood neurodevelopmental outcomes independent of the dose imbibed [193].

It may be that other risk factors such as smoking and poor nutrition also have dual effects, given the fact that they are associated with risky drinking [194] or reduced alcohol metabolism, but also with other adverse pregnancy outcomes. Hunger is common among low income South African women [195]. The possibility that poor nutrition may contribute to FAS risk in South Africa was suggested by May *et al* [196] who compared high risk women from the USA and South Africa. The American women drank more alcohol in a binge drinking pattern, but were also bigger statured, and their children had less detectable damage than the South African children. The later also found that inadequate micronutrient intake is also common in South African mothers of a FASD child [91], and have suggested that poor nutritional status, and especially low body mass index (BMI) may be a risk factor for FAS [197].

Ethnic differences in FAS prevalence have been described in the USA. Chavez *et al* [198] found the prevalence of FAS per 1000 population to be 0.6 for African Americans, 2.9 for Native Americans, 0.08 for hispanics, 0.09 for whites, and 0.03 for Asians. It remains unclear whether these differences relate primarily to differences in drinking culture, differences average SES, or other factors. Described reasons for such ethnic differences include the degree of acculturation (adaptation) of immigrants into a heavier drinking host culture, as well as the stress that accompanies this [199], discrimination or perceived discrimination [200,201], and high density of alcohol outlets in poor minority neighbourhoods [202]. In North America, binge-drinking is highest among Native Americans [203], and this is often linked to their particular history of colonial dispossession and oppression [204].

It is also possible that ethnic difference in prevalence of FAS could reflect genetic susceptibility, for example due ethnic variation in ALD isoenzymes with different pharmacokinetic properties. The evidence that ethnic groups vary in prevalence of such ALD isoenzymes [205]

supports this possibility. However, there is little direct evidence of a role for genetic susceptibility, for example a study of alcohol pharmacokinetics in mothers of children with FAS to controls for no detectable differences [206] , and the role of genetic factors remains uncertain.

It has been suggested the maternal age effects, and the variation in prevalence by ethnicity may in part be explained by the 'weathering' hypothesis [207]. This theory proposes that a range of health differences between populations, such as between African Americans and their white American counterparts of similar SES, relate to the stress and social inequalities inherent in living in a race conscious society, and the coping behaviours that people may develop including drinking itself. The theory notes that the combination of these factors can have significant pathophysiological consequences. 'Weathering' over time could explain the observed effect of a widening health differential with advancing age between black and white Americans. This includes the widening disparity in reproductive outcomes, such as neonatal mortality and low birth weight, associated with advancing maternal age [208], and perhaps also FAS[180].

Table 6: Risk factors for FAS compared to risk factors for AEP and AUD

	FAS	AEP and AUD
AGENT EXPOSURE		
Initiation of drinking	Early[25]	Early[261]
Drinking career	Long[25]	Long[261]
Drinking pattern	Binge drinking (3+ per occasion) [25]	Binge-drinking[261]
	Drinking outside of meals[25]	Drinking prior to pregnancy (AEP)[261]
	High BAC[186]	
	Failure to reduce in pregnancy[268]	
Beverage	Beer [25]	
Other substances	Frequent smoker[269,186]	Cigarette smoking[199]
	Polysubstance abuse in urban cities[25]	Poly-drug use[199]
ENVIRONMENT		
Family heavy drinking	Family of origin[25]	Any family[261]
Partner heavy drinking	Yes[25]	Yes[199]
Inter-partner violence		Yes[200]
Social isolation	Yes[25]	
Child / children	In foster care[277,199]	
	Previous child with FAS[88]	
Culture	Accepts heavy drinking[25]	
	Alcohol-centred recreation popular[25]	

Table 6 cont

Table 6 (cont):
Risk factors for FAS compared to risk factors for AEP and AUD

	FAS	AEP and AUD
HOST		
Ethnicity	SAC[25], Native American[186], African-American[267]	Caucasian[261]
Education	Low[25,186]	College level[261]
SES	Low[25,186]	Low or high[261]
Age	$\geq$ 25 years[25]	> 30 years[261]
Marital status	Unmarried, with partner[25]	Unmarried[261]
Religion	Less frequent[25]	
Reproductive	Gravidity $\geq$ 3[25]	
	Parity $\geq$ 3[25]	
	More stillbirths, miscarriages[25]	
	Late prenatal care[268]	
	Less or no prenatal care[268, 267]	
Psychological	Major depression[25]	Major depression[261,17]
	Stress, psychological distress[25,201]	Post-traumatic stress disorder[8, 17]
	Mental health problem[181]	
Injury	Accidental injury[181]	Ever physical/sexual abuse[199]
	Intentional injury (suicide attempts, abuse)[181]	Recent intimate partner violence[261, 17]
Anthropometry	Short maternal stature[269]	
	Low maternal mass[269]	
	Low BMI[269]	
Nutrition	Nutritional deficiency, change in nutritional status during pregnancy[25]	
Genetics	Particular alcohol dehydrogenase polymorphisms[25]	
Knowledge	Little awareness of FASD[25]	

1.8 PREVENTION OF FAS

The WHO Global Status Report on Alcohol and Health[6], and Babor *et al* [15] outline a range of actions countries can take to reduce alcohol related harm, ranging from broad policy and legislative approaches, to awareness-raising, to specific alcohol related health service activities, to community mobilisation. It is important that prevention of FAS should occur as part of a broader strategy to prevent the many other risks of heavy alcohol use and binge drinking, and not restrict its view to FAS in isolation.

However, FAS-specific approaches should complement broader measures. Measures to reduce peri-conceptional drinking include those targeting reduction of risky drinking in reproductive age women, and the facilitation of a planned pregnancy, for example by providing accessible contraception. Reduction of ongoing drinking in pregnancy requires early recognition of pregnancy and rapid cessation of drinking. Additional risk factors to be addressed include smoking and poor nutrition.

Despite knowledge of the considerable scale of the FASD problem for several decades, and the consensus that it is potentially completely preventable, the reality is that it remains common. Habbick *et al* [209] showed in Canada that notwithstanding major initiatives in public health and professional education the prevalence of FAS did not fall over a 20 year period. Serial surveys in an area of the Cape Winelands district of South Africa even showed an increasing trend in FAS rates, although this subsequently stabilised [139,140,167].

There is a need for demonstration of efficacy of prevention measures. Outcome measures would ideally be clinical endpoints such as rates of FAS or changes in neurodevelopmental outcome. In practice this is difficult to achieve and most existing studies have focused on changes in reported drinking, or change in risk of an alcohol exposed pregnancy.

The US IOM [72] recommends a multifaceted approach including 'universal', 'selective' and 'indicated' measures [72]. These categories are used a framework for a brief review of the literature on interventions.

1.8.1 Universal interventions

Universal measures attempt to promote the health of the general public or a particular group, regardless of risk. Within the field of FASD, the CDC Task National Task Force on Fetal Alcohol Syndrome [210] defines universal interventions as those that educate or raise public awareness of the dangers of drinking during pregnancy, or that involve broad policy or environmental change. The aim is to change social and cultural norms regarding drinking and to regulate activities and environments that promote risky alcohol use among the generally population, including women of childbearing age.

Relatively few studies have been conducted on universal prevention, and the CDC review noted that universal prevention efforts have demonstrate increased knowledge and awareness, but have generally not attempted to determine effects on alcohol consumption or risk of an AEP.

Most alcohol education programs move beyond an attempt at simple education and aim also to at persuasion to shift behaviour e.g. away from excessive drinking. Such messaging needs to compete with a variety of explicit and implication messages promoting alcohol use, especially in particular target groups which are more susceptible to advertising, such as the youth [211]. Kaskutas and Graves [212] assessed a representative sample of US adults for effects of three types of message: warning labels on drinks, warning posters in restaurants and bars, and media advertisements. They found that exposure to more types of message significantly increased rates of discussion about drinking during pregnancy, and reduced alcohol use among pregnant women.

Hankin *et al* [213] examined exposure to the warning label and its effect on drinking during pregnancy among inner-city African-American women attending a prenatal clinic. After implementation of the label law, there was a significant decrease in drinking among low-risk drinkers, but not among heavier drinkers. In a follow-up study Hankin *et al* [214] found that drinking by nulliparous women declined after exposure but there was no change among multiparous women. They concluded that multiparous women (who are often heavier drinkers) should be targeted for more intensive prevention efforts.

Glik *et al* [215] assessed the feasibility of focused marketing strategies to counter/ compete with commercial alcohol marketing as a strategy to reduce risk of have a child with FAS. Social marketing campaigns were developed with community involvement to target adolescent girls in two disadvantaged California communities (and with predominantly African American and Latina populations). They found that the African American girls had lower prior knowledge but this improved after a poster campaign, whereas the Latinas had high prior knowledge which did not increase.

In a second study, Glik *et al* [216] found that young women in disadvantaged communities receive mixed messages about dangers of drinking during pregnancy. A social norms approach using positive role models was determined to be the most acceptable message strategy based on materials pretesting. Variations in messaging, distribution strategies, and saturation levels determine whether such campaigns succeed or fail to reach priority populations. The reach of the campaign appeared better in the African-American community, and they found greater benefit in women with lower prior knowledge.

In a study using data from nearly 200,000 pregnancies included in the USA pregnancy risk assessment monitoring system (the PRAMS study), Krans *et al* [217] found that prenatal counselling regarding risk behaviour in routine care made dramatic differences to behaviour. In particular, women who used alcohol before pregnancy and who received counselling during pregnancy were much more likely to stop (72.9% vs 27.1%; P<0.01) than women who were not counselled. Even more marked differences were noted for women who had an unintended pregnancy and were counselled about postpartum contraception (83.6% vs 16.4%; <0.01) and for smokers who were counselled about smoking cessation (79.9% vs 20.1%; P<0.01).

Universal interventions may also have a much wider focus than just related to reproductive age women. For example, Holder *et al* [218] demonstrated the value of a policy and community mobilisation based approach over a 5 year period. They studied the effects of a strategy involving (1) policy changes related to sale of alcoholic beverages, age limits for alcohol use, drunk driving, and (2) community mobilization to develop community organization and support. In intervention communities compared to similar control communities, the project reduced alcohol-related motor vehicle accidents, lowered

sales to minors, and increased community support and awareness of alcohol problems.

As elsewhere, few studies on universal interventions have been conducted in South Africa. Rotheram-Borus *et al* [219] conducted a cluster-randomised trial to gauge the utility of a community health worker (CHW)-delivered integrated health promotion and behaviour change intervention. Women were recruited in pregnancy and followed up for 3 years thereafter. The study found that the alcohol use, partner violence and depression were all common, stable over time and significantly related. The intervention improved measures of mental health, and reduced alcohol use in pregnancy although women resumed afterward.

1.8.2 Selective and indicated interventions

Selective prevention strategies have focused on screening, brief intervention and referral for treatment (SBIRT). Screening is typically done using a brief scoring system such as the AUDIT, AUDIT-C, T-ACE or TWEAK as described previously. Balachova *et al* [59] demonstrated the value of a single question regarding binge drinking in the past 3 months as a predictor of AEP. These brief questionnaires aim to stratify level of drinking according to level of risk.

Brief interventions are then provided as appropriate according to level of risk. They are usually a delivered in the form of one or a few sessions lasting <15min, and may consist of professional advice, educational discussions or preferably motivational interviews. The latter approach appraises whether the person's self-perception of their drinking is congruent with the objective assessment, and the extent to which they would contemplate a change. An attempt is then made to identify their goals, for example related to child-rearing, and their drinking behaviour is reframed in this light, in order to motivate them towards stopping or reducing drinking.

Numerous studies have demonstrated the effectiveness of SBIRT approaches, reviewed by Babor *et al* [220]and Stade *et al* [221]. Furthermore, these strategies been adapted and proven effective in specific settings e.g. primary care [222] or with people living with HIV/AIDS [223] or delivered telephonically [224]. In addition they have

been adapted and proven in specific populations such as in reproductive age women, where the focus is on preventing AEP through a combination of reducing alcohol consumption and using contraception [55,225] and in pregnant women [226]. Blume [201] emphasizes the need for a greater emphasis on developing novel, culturally grounded interventions in partnership with communities.

A CDC review [210] concluded that SBIRT strategies were the most promising approach to reducing alcohol use, with success rates in multiple settings of 13-34%. From this meta-analysis, the review concluded that: (1) brief interventions can reduce alcohol use for at least 12 months among younger and older adults; (2) both younger and older adults are receptive to this approach; and (3) results remain mixed on longer term use and the reduction of alcohol-related harm. Some studies showed less apparent efficacy of the intervention in women (as opposed to men), because women were receptive even to the ultra-short intervention in the control arm.

The WHO Global Status Report on Alcohol and Health[6] states that, in view of the proven effectiveness and cost-effectiveness of SBIRT, there is a need for capacity to be increased for identification, prevention, treatment of alcohol use and AUDs, in primary care and other settings, including women who are pregnant or of child bearing age. The report makes a strong recommendation that all women be asked about alcohol and substance use at each antenatal visit (and informed of the risk), and that all pregnant women using alcohol or drugs be offered a brief intervention.

Brief interventions have also proven efficacious in South African women at risk of an AEP. Rendall-Mkosi *et al* [227] showed a halving of risk of AEP at 3 months and 12 months after a motivation intervention.

Individuals with alcohol dependency, other severe drinking problems, or who do not respond to brief intervention are referred for more extensive, indicated treatment.

Indicated interventions include rehabilitation programmes or 12 step programs such as Alcoholics Anonymous. In view of resource implications the WHO Global Status Report on Alcohol and Health[6]

recommended provision of such interventions, subject to capacity constraints.

1.8.3 Public health considerations

In making decisions about interventions, and choosing between interventions, political and public health choices need to be made. In a developing country setting questions of capacity and cost are particularly acute, but must be balanced against the very high cost and burden of disease imposed by alcohol generally, and FASD more specifically. In Canada, Popova *et al* [228] assessed the societal costs associated with FAS and FASD, which respectively have a prevalence of 0.1% and 0.9% amongst its 34 million people, as being 1.4 billion US dollars. In South Africa, a narrower assessment was made regarding costs of FAS to the health system in the Western Cape, which concluded that the cost was over USD1000 per child per year [229].

Given the scale of the alcohol and FASD problems in South Africa, there is a good case for addressing alcohol-related harm in general and FASD more specifically. The precise scope of such interventions needs to be considered. For example, Tomlinson *et al* [230] conducted a large study of pregnant Cape Town women, and found that depressed mood, alcohol use, HIV positivity and LBW were all common, and were often associated with each other. They recommended an approach that targets AEPs together with several other health problems in order to impact on multiple health outcomes.

The International Charter on the Prevention of Fetal Alcohol Spectrum Disorder [231] has powerfully outlined the scope and scale of the problem of FASD, and states the cases for targeted interventions to prevent it.

However, attempts to prevent alcohol-related harm are still at an early stage in South Africa 2017, and comprise predominantly attempts to raise awareness and reduce drunk driving. In addition, legislation is proposed to increase the drinking age to 21 years, restrict alcohol advertising and reduce the numbers of illegal taverns, since these are all considered to be cost-effective measures by the WHO [6].

It is noteworthy that there are virtually no interventions targeting prevention of alcohol use within the South African public health service. There are also no measures specifically targeting FASD, although there is concern and often sensationalistic publicity in the media. Moreover, there is a suspicion in the public health establishment that the alcohol industry favours specific issue campaigns, including campaigns against FASD, because this would have less effect on their bottom-line than broader legislative approaches [232].

1.9 THE SOUTH AFRICAN CONTEXT

1.9.1 A snapshot of relevant history

The two main ancestral populations of South Africa were the Khoisan, who were the first people of southern Africa, and several BSA tribes who migrated into the eastern half of the geographical area within the last few millennia.

The Dutch East India Company established a settlement in the south-western tip of Africa in 1652. This became Cape Town, and was the centre of a growing colonial presence than initially impacted on Khoisan society, which collapsed within the course of a few generations as a result of conflict over land, and epidemics of imported diseases such as smallpox.

The current SAC population is a highly admixed population that developed during successive periods of colonization by the Dutch and British (between 1652 and 1910). This population derives from a variety of ancestral sources: the historical and genomic records [233] concur that the major ancestries are Khoisan, European, black African (predominantly slaves from East Africa) and Asian (slaves or political exiles from South Asia and the Dutch East Indies). The nascent SAC population was subject to discriminatory laws throughout the colonial period.

In the 1870s diamonds were discovered in Kimberley, and a decade later gold was found in the Witwatersrand. This led to the industrialisation of the interior of South Africa. The BSA population had, since the early 1800s come into conflict with the expanding frontier of the Cape colony and with boers who trekked into the interior, but now laws such as the 1913 Land Act were used to drive the BSA population off much of their land in order to provide workers for industry.

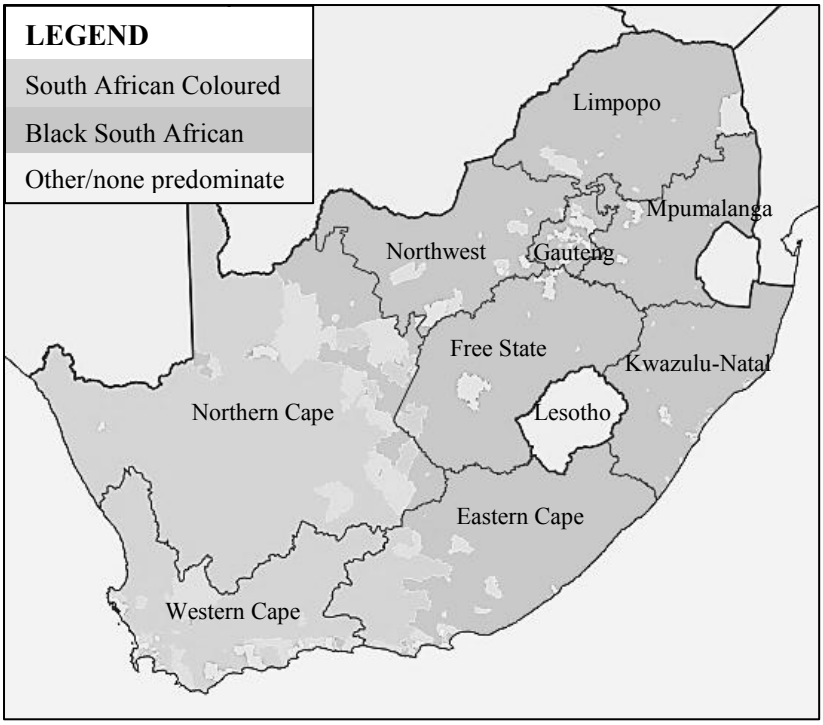
The position of the BSA population worsened under Apartheid when they occupied the bottom rung in a rigid racial hierarchy. During this time the SAC were co-opted by giving them an intermediate status in the hierarchy, and by giving them labour preference in the Cape of Good Hope Province (the area of the former Cape Colony, that

includes the current Western Cape Province and Northern Cape Province).

In the Apartheid era, legislation was implemented to minimise the influx of black South Africans to urban areas, and segregation of urban areas by population group was strictly enforced by the Group Areas Act. If BSA citizens were allowed into urban areas at all, they were required to live in a township (an outlying suburb designated for this population group). Such townships were developed alongside all South African towns and cities.

Following a prolonged struggle, democracy was achieved in 1994. The post-Apartheid period has presented massive new challenges such as HIV/AIDS, but at the same time South Africa remains burdened by its colonial past. While much has been achieved, South Africa remains one of the world's most inequitable societies, and race remains an important proxy for social class. While the middle class has de-racialised significantly, the great majority of the poor and working class are BSA or SAC. As shown in Figure 4, the SAC population predominates in the western half of the country. This corresponds roughly to the former Cape Colony, the area of which now includes the WCP and most of the Northern Cape Province (NCP). The BSA population predominates in the rest of South Africa, which is more heavily populated.

Figure 4: Most populous population group, by electoral ward



(From: https://en.wikipedia.org/wiki/Demographics_of_South_Africa)

1.9.2 A snapshot of historical alcohol use in South Africa

At the time of colonisation the Khoisan did not have a tradition of alcohol production, but alcohol played an important role from the earliest years of the Cape Colony, as indigenous pastoralist and coastal peoples were induced to enter service on settler farms with payment of tobacco, bread and wine. In the early years of the colony the Dop (tot) system developed, by which farmworkers, who were also often slaves until the 1830s, were provided a daily measure of

alcohol [234]. The Dop system subsequently became part of farming practice until recent times, and served as an important element of social control as well as being a market for low grade alcohol products [235].

There is considerable evidence that the Dop system has been instrumental in the very high local levels of risky drinking. For example, a study by London [236] found that 19% of the farmworkers in the Witzenberg area of the Cape Winelands were currently receiving Dop, and nearly half had ever been exposed to it. Those exposed to Dop were nearly 10-fold less likely to be abstainers than others.

While the Dop system is generally perceived to be associated with the Cape Winelands, and with wine farms, studies in the Cape Winelands district conducted on wine, fruit and vegetable farms, found the provision of Dop to vary from 6% to 20%, with the higher rates on smaller farms and non-viticulture farms [235,237]. In addition, legislation permitted provision of alcohol as part of the wage until 1961, throughout the old Cape of Good Hope Province (which comprised mainly the current Western and Northern Cape provinces) until 1961. Loopholes allowed for provision of Dop until the 1990s.

Given its long history, the Dop came to play a significant cultural role in farming communities of the Cape Colony. The historian Pamela Scully wrote that "Under the extremely oppressive conditions under which farm workers laboured in the 19th century, the consumption of the daily dop created… a social focus around which farm workers could construct their own cultural identity. Farmers might supply the wine but they could not fully determine the interaction that took place… " (quoted in London, 1999 [225]).

Although the Dop system has now been virtually eliminated [48] it seems certain that the legacy of the system remains an important determinant of drinking practices. Among the predominantly SAC workers on farms in the Western Cape, Falletisch [234] describes weekend binge-drinking as being most commonly a group activity, often serving to unite and promote friendship, with little to no support to stop drinking among many peer groups, and little belief that their drinking is a problem.

Even in the absence of the Dop, farmworkers are a particularly

vulnerable group. Labour conditions on farms have historically been among the poorest of all employment sectors [238] , farmworkers are disempowered by a culture of paternalism [239], and the general health status of farm workers is extremely poor with growth stunting occurring in 30% - about double the average for urban children [234]. Female farm workers are particularly vulnerable, often only being given casual employment at the time of harvest, or having no option of doing lighter tasks in pregnancy [240].

Outside the Western and Northern Cape provinces, the BSA population predominates in both rural and urban areas. The BSA community had a pre-colonial drinking culture, with women responsible for brewing sorghum beer that had an alcohol content of 1-2%. Although women brewed beer, there were strong traditional prohibitions on women drinking at least until their middle adulthood [241].

An additional factor is that the Dop system was not implemented outside of the erstwhile Cape Colony, in part because labour needs were different. Government policies were not uniform, but often aimed to control access of workers to alcohol e.g. through establishment of government beerhalls with a monopoly to provide alcohol (unpublished data, Lunderstedt S, 2000). In these circumstances illegal bars, or shebeens, became prevalent in urban areas.

In summary, historical forces have created a situation in which drinking practices of women might be expected to differ based on social class, province of residence, and population group. In addition, the effect of residence in urban or rural areas may be expected to differ in the SAC and BSA population groups. These expectations tie in well with the data provided earlier regarding female drinking practices (see section 1.3.1 and 1.3.2).

CHAPTER 2: OBJECTIVES

2.1 JUSTIFICATION

Fetal alcohol syndrome has been shown to be an important public health problem in the Cape Winelands district of the Western Cape [139,140,167]. However, the laborious nature and cost of FAS prevalence surveys has meant that little information has been available elsewhere South Africa. Similarly, information regarding mothers of children with FAS has been limited to the Cape Winelands.

High levels of alcohol consumption in a binge-drinking pattern have been demonstrated in other areas of the Western Cape Province [63,177]. Within South Africa at large, rates of female binge drinking have been shown to vary by province, and by woman's ethnicity, age, educational level, and by urban or rural residence [44,45,49]. Although female drinking patterns may suggest a risk of FAS elsewhere in South Africa, a direct correlation between the two cannot be assumed.

There is a need to determine the prevalence of FAS in non-viticulture areas of the Western Cape Province, in other provinces of South Africa, among residents of cities rather than rural areas or small towns, and in ethnic groups other than SAC, especially the majority BSA population of South Africa, and in other suspected high risk groups.

More information is also required regarding neurodevelopmental outcomes of children with FAS and other children prenatally exposed to alcohol, in the context of low SES communities in a developing country.

Additional information is also needed to identify the optimal approaches to prevention of FAS. This includes information regarding maternal risk factors for FAS across a range of settings, an assessment of the extent to which drinking practices are open to change in this high-risk group of women, identification of potential approaches to intervention, and studies to directly evaluate interventions to prevent maternal drinking and FAS in South African settings.

2.2 GENERAL OBJECTIVES

1. To determine the extent of FAS as a public health problem across a range of South African environments and populations.
2. To describe and compare mothers of children with FAS across a range of settings. Identification of risk factors, especially those that are modifiable, will inform the relevance of different approaches to prevention.
3. To assess childhood developmental outcomes associated with heavy maternal alcohol use.
4. To investigate the potential for prevention of FAS in South African settings.

2.3 SPECIFIC OBJECTIVES

1. To determine the prevalence of FAS in several sites in the Northern Cape Province of South Africa using an active case-ascertainment methodology.
2. To determine the prevalence of FAS in city residents, comparing areas of predominantly SAC and BSA ethnicity.
3. To determine the prevalence of FAS in several sites in the Western Cape Province using an active case-ascertainment methodology.
4. To make an inter-site comparison of mothers to a child with FAS regarding a range of risk factors for the condition, including alcohol use and change in drinking practice.
5. To assess the extent to which FAS prevalence is congruent with national data sources on drinking patterns.
6. To identify factors relevant to prevention of FAS in various South African settings.
7. To compare neurodevelopment outcomes of children with FAS to other children prenatal exposed to alcohol, and to controls.
8. To assess the impact on prevalence of FAS of an intervention aimed at primary prevention by improving community awareness.

CHAPTER 3: METHODS AND PROCEDURES

3.1 Study settings, population, and research group

3.1.1 Snapshot of South Africa, and the study provinces

SA is an upper middle income, of 52 million, with a largely resource based economy. By Gini coefficient, it is considered one of the world's most economically unequal countries. It is also very ethnically diverse: the national census of 2011 counted almost 52 million South Africans, of whom 79% were BSA, 9% were SAC, 9% 'White' and 3% Asian [242].

Overall, Gauteng is by far the largest provincial economy, and is the smallest but most populous and cosmopolitan province. It includes the national capital city Pretoria, and the economic heartland Johannesburg has an economy largely based on manufacturing, financial services and mining.

The Western Cape is the fourth largest province by surface area and population (5,8 million), and the joint second largest provincial economy. By Gini coefficient it is slightly less economically unequal than the national average, and is the province with the highest human development index. Agriculture comprises only 5% of the WCP economy but a majority of its exports, in the form of wine, grapes and other fruit. (https://en.wikipedia.org/wiki/Economy_of_the_Western_Cape)

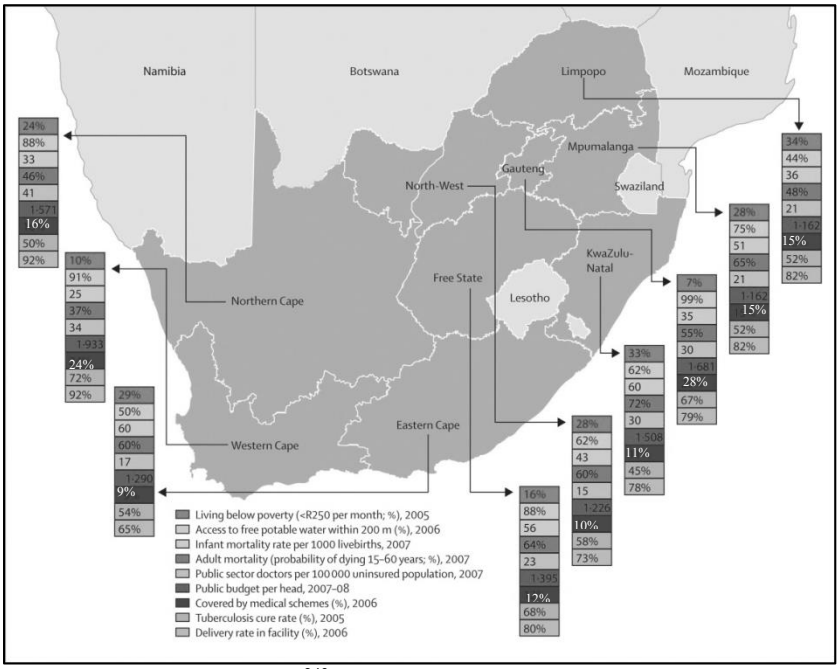
The Northern Cape is the largest province, but is arid and has a very low population density, with a total population of 1,145,000. It is a small contributor to the SA economy, especially given the reduced

production in the Kimberley diamond mines in recent decades. The main components of economy are mining and agriculture, which includes sheep farming and grape production on the banks of the Gariep River.

(http://www.southafrica.info/about/geography/northern-cape.htm#.VrWmSvl94gs)

Figure 5 provides data regarding current indicators relevant to health for the Western Cape and Northern Cape in comparison to South Africa's other provinces.

Figure 5: Indicators for health and development in South Africa's provinces

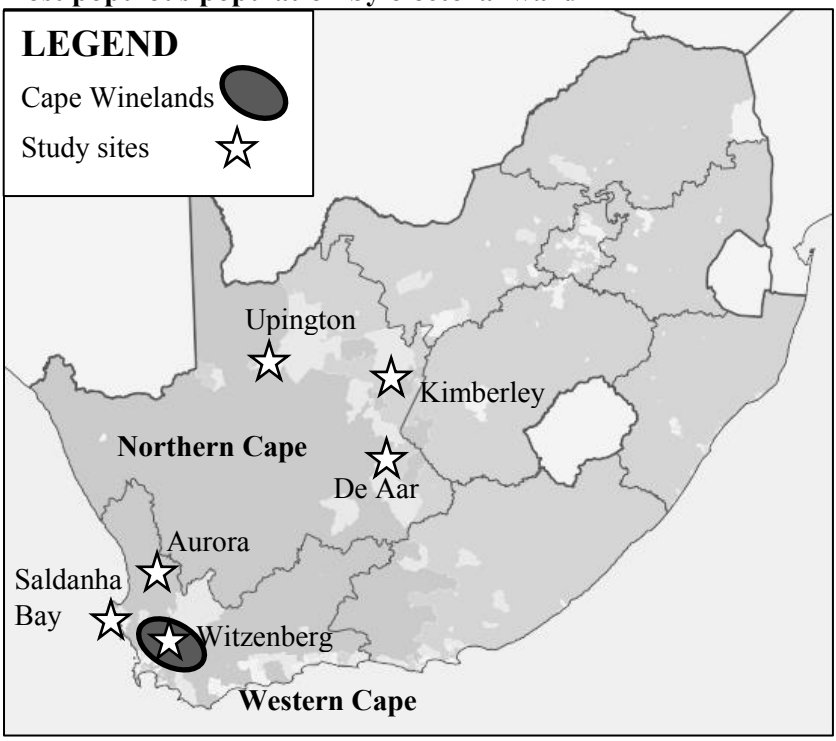


(From Coovadia *et al*, 2009 [243])

3.1.2 Overview of study sites

The location of the study sites within the Western and Northern Cape provinces, and in relation to the Cape Winelands, is shown in Figure 6.

Figure 6: South Africa, showing provinces, study sites and most populous population by electoral ward



Ref: https://en.wikipedia.org/wiki/Demographics_of_South_Africa

3.1.3 Sites in the Northern Cape

De Aar town **(study 1, 5, 6, 7)** is the 9th largest town in the NCP, with a population of 42,000 (Statistics South Africa, 2012). The town is in an isolated, arid region. It had historically been an important railway junction, but the railways have reduced in importance over time. Economic activity relates to the railways, sheep farming and, since

the studies were conducted, large-scale solar farms have been developed in the area.

Upington town **(study 1, 5)** is the 3rd largest urban area in NCP, with a population 93,000 [242]. It is on the banks of the Gariep River and is a tourist town and a centre of vilticulture, produces wine and table grapes.

Kimberley **(study 2, study 4)** is the capital of the Northern Cape Province and is one of the secondary cities of South African. It has 236,000 inhabitants [242] , and is among the oldest towns in the interior of the country. It developed during the diamond rush of the 1870s. Diamond mining has since been the backbone of its economy, which has stagnated in recent decades due to downscaling of mining operations. The suburbs of Kimberley include Galeshewe and Roodepan.

Galeshewe developed during the diamond rush and is among the oldest "townships" in South Africa, dating to the 1880s. The term township refers to a high-density suburb set aside for Black South Africans, often in the apartheid era). It has a population of 118,000 people (Sol Plaatjie Municipality, unpublished data) with an ethnic composition of 92% Black African, 7% Coloured, and <1% other. By first spoken language, the composition is as follows: 71% indigenous African languages, 25% Afrikaans, and 3% English [242]. Most housing is formal and it is relatively well serviced. There is little economic activity in Galeshewe itself, and a high level of unemployment and concomitant social problems including risky drinking and domestic violence (Botes A, Northern Cape Department of Social Development, unpublished data).

Roodepan was established as an area for Coloured people under the Apartheid Group Areas Act in 1975 (B. Nagel, Africana Museum, Kimberley, unpublished data). Although of much more recent origin than Galeshewe, Roodepan is characterized by similar socioeconomic conditions. The population of 27,500 people (Sol Plaatjie Municipality, unpublished data) is predominantly of Coloured ethnicity (83%), with 12% Black African and 5% other. Afrikaans is the first spoken language for 84%, 5% speak indigenous African languages, 9% English, and 2% other [242].

3.1.4 Sites in the Western Cape

Aurora **(study 3)** is a rural village of approximately 2 500 inhabitants. Employment is mainly as seasonal labour for surrounding potato and grain farms. There is one school in the area (grades 0 - 7), at which the parents/guardians of all learners were invited to enrol in the study.

Witzenberg district **(study 4)** is a viticulture and fruit farming region in the Cape Winelands district, where the 'Dop' system was widespread until recent times[244]. The survey was conducted at 18 primary schools in the town of Ceres (population 30,000), several smaller towns, or on farms.

Saldanha Bay district **(study 4)** includes the town of Vredenburg (population 38,000), the harbour town of Saldanha Bay (population 28,000), and surrounding coastal villages. Economic activity relates predominantly to shipping and fishing. At all three sites in the Western Cape, the population is predominantly of SAC ancestry.

3.1.5 Research group

The research team for the studies presented in this thesis was brought together by the Foundation for Alcohol Related Research (FARR). FARR is a not-for-profit organization that includes a range of health professionals who provide a variety of resources related to alcohol and health.

FARR works primarily with government departments, in particular the Departments of Social Development, Education and Health. In particular, FARR has a team that conducts FAS prevalence surveys, and another that provides awareness-raising and educational activities. The studies were funded by the relevant Departments of Social Development, or specific research organizations. Ethical approval for the studies was obtained from the Departments of Education, Health and Social Development at district and provincial level.

Another aspect of FARR's work is to support and advocate for children, family and communities affected by FASD. This is an ethical necessity in doing work on FASD. Linked to each prevalence

survey, FARR provides education to communities and professionals alike about FASD and how it can be prevented and ameliorated.

FARR has established a community support group for families with a FAS child, which is based in Cape Town, and FARR has had an ongoing site in De Aar since the late 1990's. These provide ongoing support options, but much more needs to be done to obtain national reach. During the course of studies in individual towns or districts, a local office is established for the duration of the study. Amongst other functions it provides information and support to study participants.

3.2 STUDY DESIGN

3.2.1 Design: Prevalence surveys (study 1, 2, 3)

The FAS prevalence surveys aimed to make an accurate assessment of the prevalence of FAS and partial FAS in several defined geographical areas. An active case ascertainment approach was used, which was similar in each study. It entailed a tiered screening process involving all first grade learners at the selected primary schools.

Agreement to the study, and associated educational activities, was made at a provincial or district level. School principals were then involved, and consent was sought from parents.

Anthropometric measurements were obtained for all children with consent. Those who screened positive on anthropometry received a clinical and dysmorphological assessment.

Learners with a positive clinical assessment were requested to return for a neurodevelopmental assessment, using the Griffiths Mental Development Scales (GMDS) or similar standard methodology.

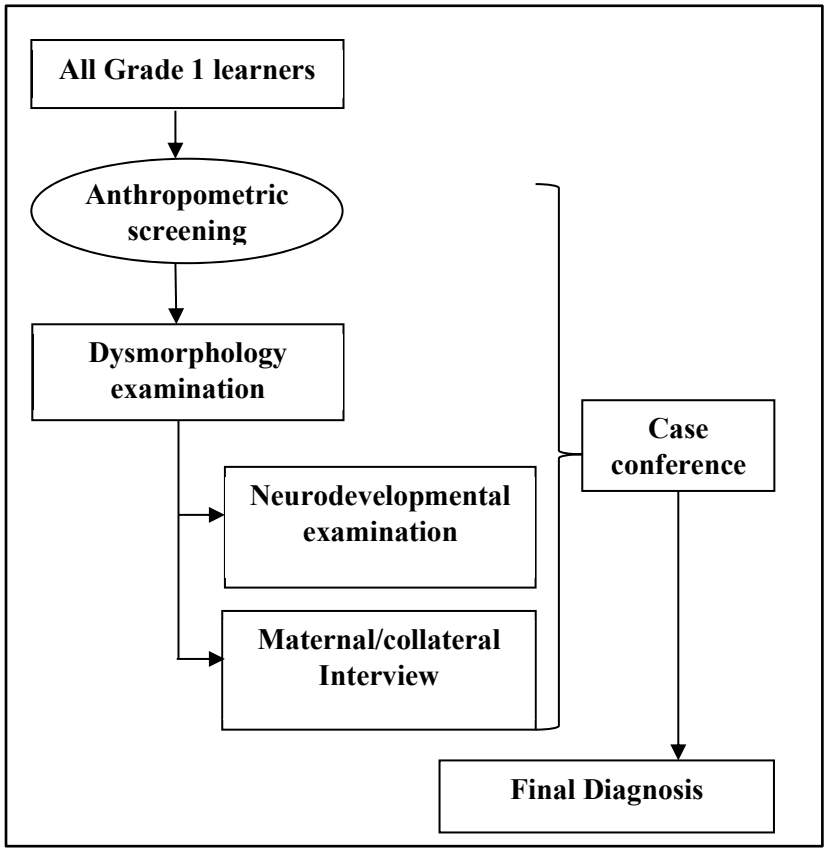
In addition, their mother or if necessary a proxy/collateral informant was asked to return for an interview, which followed a structured format.

In study 1, one site in study 4, and study 6, a control group was selected for comparative purposes. For cost reasons, this was not possible for all studies or sites.

After information had been gathered for all the above domains, a case conference was held to synthesise the information into a final diagnosis. With consent, the diagnosis was returned to the parents.

The tiered process is outlined in Figure 7 below.

Figure 7: Tiered diagnostic approach to FAS diagnosis



3.2.2 Design: Cross-site questionnaire survey (study 4)

Maternal interviews, using a structured questionnaire, are conducted as part of FAS prevalence surveys. They contain, in addition to information on drinking practices, extensive information pertaining to demographic and reproductive variables, and other known and putative risk factors for FAS. In addition, anthropometric measurements are obtained for mothers.

We compared questionnaire data and maternal anthropometry obtained from 3 prevalence surveys conducted at widely divergent sites: the Witzenberg sub-district (urban/rural) and the Saldanha Bay sub-district (mainly urban) in the Western Cape, to a subset of women from Kimberley (urban) in the Northern Cape. The overall FAS prevalence rate was high for all three sites, in the region of 5%. For comparative purposes a control group was available from the Saldanha Bay site.

The FAS prevalence at the Witzenberg and Saldanha Bay sites were previously unpublished, and this study therefore also augments the published literature on FAS prevalence in the Western Cape Province.

For this study, we selected interviews with mothers (or collaterals) of children who were of the SAC population group, in order to further explore the risk factors for FAS in this apparently high-risk population, with a view to comparing similarities and differences between sites, and to look for factors most pertinent to preventive interventions in the SAC population.

3.2.3 Design: Pre-post intervention study (study 5)

The aim of this study in the de Aar and Upington sites was to assess the efficacy of an awareness-raising and educational intervention in reducing prevalence of FAS and related risk factors. Comparison of FAS/PFAS prevalence before and after the intervention was selected as the primary outcome measure. Secondary outcomes were: maternal knowledge about harms of alcohol use during pregnancy; self-report

of maternal alcohol consumption; birth weight; infant anthropometry; neurodevelopment subscales and dysmorphology scores.

There were three study phases. The initial phase included an assessment of P/FAS prevalence among infants born in a one year interval, and a questionnaire to assess maternal knowledge regarding FAS and the risks of alcohol use. The methods were adapted from those used in our surveys of school entry children.

In the following year, a suite of prevention interventions was implemented, focusing on awareness-raising and education in the community and particularly the antenatal clinics.

A year later, the third phase included assessment of prevalence of FAS and maternal knowledge for a second one-year birth cohort.

In both phase 1 and phase 3 we attempted to trace all children born at the local public sector hospitals in de Aar. As Upington has a larger population, a random sample of about half the children was selected from a list of all births in each 1-year period.

It should be noted that a subset of participants at the de Aar site were followed up for further neurodevelopment assessment at 18 months and 5 years of age. Publications are included in the Annexure as studies 6 and 7.

3.3 STUDY POPULATIONS AND SAMPLING

3.3.1 Samples: Prevalence surveys (study 1, 2, 3)

FAS prevalence surveys were conducted among first grade learners attending selected primary schools at several sites in the Northern Cape and Western Cape provinces.

Study 1 assessed the prevalence of P/FAS in De Aar and Upington in the Northern Cape. All primary schools in the lower income suburbs

that had previously been reserved for people of BSA or SAC population groups under Apartheid were included. A total of 536 learners were included from eight primary schools in De Aar, and 1299 learners from 15 primary schools in Upington.

Study 2 compared the prevalence of P/FAS in two suburbs of Kimberley in the Northern Cape. This is relevant because under Apartheid the two suburbs, Galeshewe and Roodepan, had been set aside for the BSA and SAC groups respectively, and remained largely segregated in the same manner at the time of study. A total of 1587 learners were eligible for inclusion, and consent was obtained for 1510.

Study 3 assessed the prevalence of P/FAS in the isolated village of Aurora in the Western Cape. This study differed in that only a single primary school was assessed, but learners in all school grades were assessed. A total of 171 learners were eligible for inclusion, and consent was obtained for 160.

Study 4 included prevalence surveys conducted at all primary schools in the Saldanha Bay sub-district and the Witzenberg sub-district of the Western Cape. At total of 1540 learners were enrolled in Saldanha Bay and 1010 in Witzenberg.

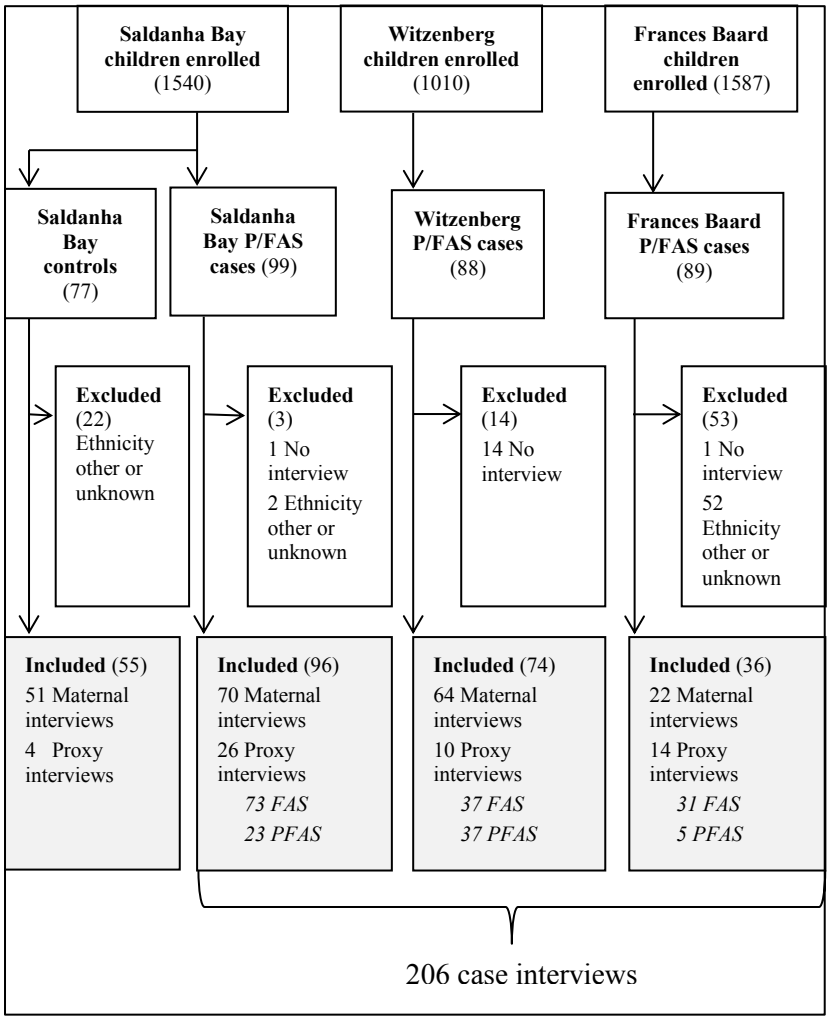
3.3.2 Samples: Cross site questionnaire survey (study 4)

FAS prevalence surveys conducted under the auspices of FARR were included in this study if they used an identical approach to FAS diagnosis (described by Hoyme *et al* 2005 [74]), and enrolled a representative group of school-entry children. Three surveys met these criteria. In chronological order these were the surveys in Witzenberg sub-district conducted in 2008, in Kimberley municipality conducted in 2012, and in Saldanha Bay sub-district conducted in 2013.

All interviews at the three study sites pertaining to learners who were of SAC ancestry were eligible for inclusion in the study. Figure 8 outlines the process by which interviews were included and excluded.

A total of 206 interviews related to FAS cases were included, as well as 55 control interviews. Case interviews were with mothers in 156 instances (76%), and with collateral informants in 50 (24%).

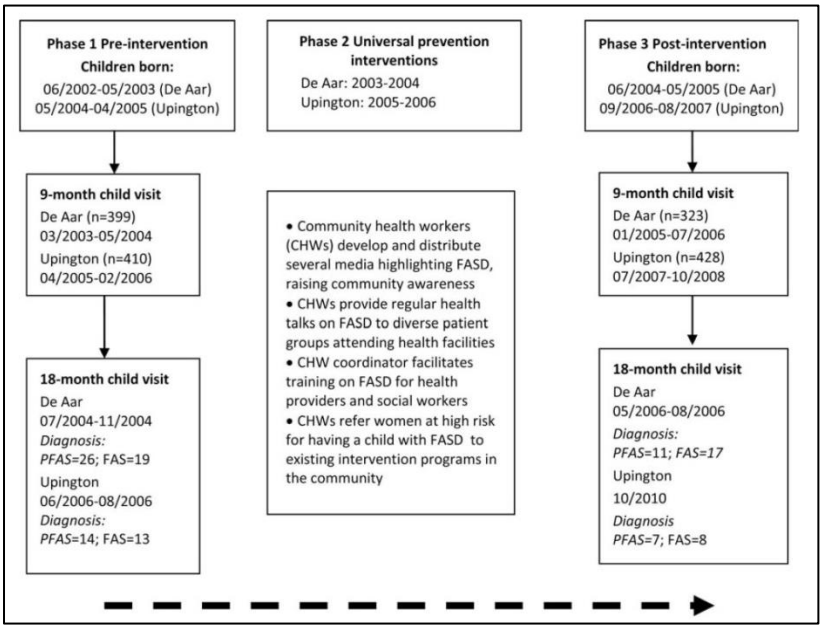
Figure 8: Flowchart of participants for cross-site questionnaire survey



3.3.3 Samples: Pre-post intervention study (study 5)

Figure 9 outlines the samples in the different phases of study 5. Prior to the intervention a birth cohort of 399 infants was obtained in De Aar, and 410 infants in Upington. Following the intervention a birth cohort of 323 infants was obtained in De Aar, and 428 infants in Upington. In both cases the whole cohort was assessed at a 9 month visit, and those with suspected P/FAS were reviewed at an 18 month visit alongside control infants.

Figure 9: Flowchart of the 3 phases of the pre-post prevention study



3.4 STUDY PROCEDURES

3.4.1 Procedures: Prevalence surveys (study 1, 2, 3)

Anthropometric screening

The initial screening phase includes anthropometric measurements (height, weight and head circumference for all children). Learners screen positive if their (1) height and mass are <10th centile [245] or (2) head circumference is <10th centile [246].

Screen positive individuals receive clinical assessment with particular emphasis on dysmorphic and neurological features.

Clinical and Dysmorphology assessment

Dysmorphology assessment is performed by medical geneticist for the three primary facial features that are essential to the diagnosis of FAS and partial FAS: short palpebral fissures, smooth philtrum and narrow upper vermilion border [74]. The assessment of the upper lip is assisted by use of a photographic Likert scale showing the range of normal upper lip appearance, and features consistent with FAS.

Further dysmorphic evaluation is conducted for a range of other minor dysmorphic features associated with FAS, as well as severe birth defects that are more common with prenatal alcohol exposure. The number of unusual anthropometric features and dysmorphic features is summed to yield a dysmorphology score [74]. This is used as supportive evidence for the diagnosis. Table 3 in section 1.5.5 of the literature review outlines the minor dysmorphic features and major anomalies associated with FASD.

In addition, the patient is assessed for 'hard' neurological signs, and for any signs of ill health that would warrant referral to a health provider.

If the clinician is concerned about the possibility of P/FAS, the child receives a full neurodevelopmental assessment and an interview is performed with the mother or collateral informant. If the clinician is

worried about another syndromic diagnosis, the child is referred for further investigation.

Neurodevelopmental assessment

Neurodevelopmental assessments are conducted by a registered psychometrist using standard methods, though the specific methods changed during the study period.

In study 1, ten developmental domains were tested with individual subscales, all of which had been previously used in South Africa and eight of which had been validated in South African populations (excluding the first two in the list): DAP Goodenough-Harris – standard (estimated intellectual development), Raven's coloured progressive matrices (non-verbal reasoning), test for reception of grammar – standard (grammatical contrasts and language comprehension), visual motor integration – standard, motor coordination – standard, visual perception – standard (tests ability to perceive visual information), word association/similarities – standard (tests auditory perception, concepts belonging together and verbal comprehension), absurdities/missing parts – standard (tests visual perception and cognitive evaluation of stimuli), story memory – standard (tests short-term memory and attention), digit span – standard (tests short-term memory and information encoding).

For practical reasons this was replaced for all other studies with a standard test, the Griffiths Mental Developmental Scales (GMDS). The GMDS can be used to assess the neurodevelopment of children up to a functional level of eight years age [247,248]. The GMDS and the GMDS-Extended and Revised (GMDS-ER) have been widely used in South Africa [249,250]. In addition it has been used locally by ourselves and other authors in the assessment of children with FASD [109,251].

The GMDS assesses six developmental domains from infancy to middle childhood. The General Quotient (GQ) is a composite of the six subscale scores, namely: Locomotor (gross motor skills), Personal-Social (adaptive functioning), Hearing-Speech (verbal ability), Eye-Hand (fine-motor co-ordination), Performance (pattern construction and speed of performance) and Practical Reasoning (numerical, time and spatial concepts).

Raw scores are converted into z-scores for each subscale as well as for the GQ. The z-score was considered normal if between 0 and -0.49, mildly delayed between -0.5 and -0.99, delayed between -1.0 and -1.99 and severely delayed if <-2.00 [252]. Neurodevelopment was considered delayed if the z-score for either the GQ or for at least two subscales was significantly delayed.

For interpretation purposes it should be noted that developmental score ranges in the Griffiths score are not identical to those of intelligence quotient instruments, and also vary between the different subscales [253]. For example, the upper bounds of the mild intellectual disability range (IQ score 69) and the borderline range (IQ score 79), for Griffiths test are: 74 and 82 for GQ, 63 and 75 for language, and 68 and 79 for hand-eye coordination, 64 and 76 for performance, and 64 and 75 for practical reasoning. This should be borne in mind when assessing Griffiths test scores.

Maternal interviews

The maternal interview questions were modified from a structured maternal questionnaire first developed for populations in the southwestern USA. They were adapted specifically for the South African situation, and made available in both English and Afrikaans (the language most widely spoken in the SAC community). The questionnaire was pilot tested in a target community [138]. The initial questionnaire contained 114 items covering basic demographics such as residence, religion and ethnicity, social and economic variables, reproductive health, and the family health, diet and substance use. The questions aimed to reconstruct women's lives and alcohol use over time. To establish rapport non-threatening questions were asked first, followed by more specific questions about alcohol.

In the alcohol section, interviewees were first asked about drinking habits of family members and friends. Then the details of the mothers drinking were discussed, first for a recent 1 week period, quantifying the amount she consumed daily in standard drinks. Pictures of standard beer bottles or other containers were used as reminders. Such approaches are particularly important in a South African setting due to the limited functional literacy of many study participants. Current drinking was used as a benchmark to compare drinking practices for the time just before the mother recognised her pregnancy, and then

for each trimester of pregnancy, and for the months following pregnancy.

The questionnaire was subsequently revised to shorten the interviewing process (Strauss, unpublished data). The number of questions was reduced to 101 items, by decreasing the number of free text probes and by aggregating or omitting some items. The revised version was used for the Kimberley and Saldanha Bay sites. In addition, an abbreviated version of the interview was developed for collateral informants. With either version of the interview, information was less complete from proxies than mothers, causing variation in the denominator between study variables.

Interviewers were professional study staff or community workers who were trained as interviewers, and accountable to the site supervisor. Interviews were conducted with the mother of the index case, or a proxy informant (usually close family member) if the mother was unavailable after two tracing attempts.

Case conference

The final aspect of the diagnostic process is a case conference at which the different sources of case information are synthesised to assign a final diagnosis by consensus. The case conference involves all relevant parties – clinicians, psychometrists, interviewers and site supervisors. Diagnoses of FAS and partial FAS were made using the classification of Hoyme *et al* (2005).

The possible final diagnoses assigned at the case conference are:

- FAS
- Partial FAS
- Drank during pregnancy, child has one or more key feature, but not FAS or partial FAS
- Drank during pregnancy: no apparent FASD
- Did not drink during pregnancy: not FASD
- Other diagnosis e.g. other syndrome or intellectual disability unrelated to FAS

3.4.2 Procedures: Cross-site questionnaire survey (study 4)

The FAS prevalence questionnaires and interview process has been described in section 3.2.1 above. The questionnaire data selected from the three different sites were merged onto a single study database to facilitate analysis.

Although many variables were identical between sites, the merging process was not straightforward. The revision of the questionnaire between the first and second FAS prevalence surveys included meant that some questions could not be merged and were omitted. In addition, a number of variables could only be analysed after recoding to create a common variable between all sites. Difficulties included the fact that a variable may be named differently in different databases. These could only be merged after it was confirmed they contained identical information. Where the information was collected differently, it needed to be determined if there was a method to create a common variable, for example by appropriate categorisation of variables. In some instances free text fields in the MS Excel database needed to be manually reviewed to create a comparable structured field.

3.4.3 Procedures: Pre-post intervention study (study 5)

Phase 1 and 3: assessing study outcomes before and after intervention

Identical procedures were used in both phase 1 and phase 3. Birth weight was obtained from hospital records. An initial FAS assessment was conducted at approximately 9 months of age for all enrolled infants. This used the same tiered method as in the school prevalence surveys, with all study procedures being adapted to the much younger age-group of the participants. The anthropometric measurements used the same centile cut-offs, the same checklist was used for dysmorphic features, the GMDS was used for neurodevelopmental assessments, and the maternal or collateral interview was unchanged. In addition, Beck's Depression Inventory was used to screen for maternal depression [254,255].

Participants who were positive on anthropometric screening criteria received a clinical, dysmorphic and neurological assessment. Those with dysmorphic features suggestive of FAS received a neurodevelopmental assessment and a maternal interview. A follow-up dysmorphic and GMDS assessment was performed at an 18 month visit for participants who were suspected of having P/FAS. Final diagnoses were made at a case conference.

Phase 2: Universal FASD prevention interventions

In phase two, universal FASD prevention activities were provided using multiple platforms, over 1 year (Figure 9). Three trained CHWs led activities in each site. They received a monthly stipend and were supervised by full-time study coordinators (professional nurses).

With input from local community representatives, a pamphlet and poster were designed and distributed to antenatal clinics, shops, taverns, government departments and prisons. Regular articles focusing on FASD prevention, and emphasising the responsibility of both parents and the community for its prevention, were published in local community newspapers and reinforced by regular advertisements on the local community radio. Local drama productions on FASD themes were performed.

The CHWs presented health talks at antenatal clinics, child health clinics and family planning clinics, as well as community and church meetings. These addressed a range of topics such as nutrition, breastfeeding and family spacing, but were always underscored by messaging on FASD prevention.

Training workshops on FASD were held for provincial and district-level staff from the Departments of Health and Social Services. FASD prevention messages were mainstreamed within the Department of Health's activities and in their interactions with the public, with FASD topics given prominence in all National Health Promotion events, such as Women's Day, Pregnancy Education Week, International FASD Day and Breast Cancer Awareness Month.

3.5 DATA MANAGEMENT AND ANALYSIS

3.5.1 Data management and analysis: Prevalence surveys (study 1, 2, 3)

Single data entry was conducted using a study database created in Microsoft Excel (Microsoft, Redmond, WA, USA). Prior to analysis the database was cleaned by looking for and correcting missing and outlying variables. Missing data resulted in some denominator differences between different variables. For interview data, these most often arose from the fact that collateral informants were unable to answer all questions.

Univariate analysis was performed using Intercooled Stata (Statacorp, LP, College Station, TX, USA). For analysis of continuous variables, we used an unpaired Student's t-test or Mann–Whitney U-test for normally and non-normally distributed data, respectively. The Mantel–Haenszel chi-square or Fisher's exact tests were used for analysis of categorical data. These tests were used to identify differences between comparator groups: cases and controls in study 1, cases from Roodepan and Galeshewe in study 2.

3.5.2 Data management and analysis: Cross-site questionnaire survey (study 4)

Using data from three prevalence surveys, intercooled Stata 13 (StataCorp, LP, College Station, TX, USA) was used to merge and recode questionnaire databases from the individual study sites, and to conduct statistical analysis. Univariate analysis compared controls to all cases – this was the main focus of the study and was presented in the tables. In addition, cases were compared between the three sites, and findings were discussed in the text if they illustrated key points relevant to a future intervention.

Categorical data was analysed using the Pearson chi square, or the Fisher exact test for samples with few values in a cell. Ordinal and

continuous data was analysed with the Student's t, Kruskal-Wallis or one-way Anova, tests as applicable.

3.5.3 Data: Pre-post intervention study (study 5)

Single data entry was done in a Microsoft Access 2003 (Microsoft, Redmond, WA, USA) database, and Intercooled Stata version 10.1 (Stata-Corp, LP, College Station, TX, USA) used for analysis.

Univariate analysis to detect differences between categorical variables was conducted with the chi-squared test, and the chi-squared for trend was used to determine if there was an increasing trend in proportions over exposure categories. For continuous variables, an unpaired Student's t-test or Mann–Whitney U-test compared data with a normal and non-normal distribution respectively. Infant anthropometric data were analysed using z-scores computed with the WHO Child Growth Standards program in Stata (http://www.who.int/childgrowth/software/en/).

Multivariate logistic regression models were used to investigate whether study phase was associated with P/FAS diagnosis, controlling for maternal age, ethnicity and study site. As other socio-demographic data were only collected in a population subset (P/FAS cases and controls) these variables were not included in multivariate models.

3.6 ETHICAL CONSIDERATIONS

3.6.1 Ethics: IRB approvals

FARR collaborates with academic institutions. The studies presented in this thesis were performed together with collaborators at the Universities of Stellenbosch and the Witwatersrand, and in the case of study 5, with the US Centers for Disease Control. Approval for the studies was given by the Research Ethics Committees of the University of the Witwatersrand (study 1, 5, 6, 7) and the University of Stellenbosch (study 2, 3, 4).

3.6.2 Ethics: study activities and referrals for care

Study participants with developmental deficits, health and social problems need to be referred to local professionals, including speech and hearing therapists, occupational therapists and physiotherapists, school psychologists and health care facilities. This permits children with new diagnoses to obtain the locally available optimal standard of care, which would not have been possible in the absence of a diagnosis. Permission was obtained from the provincial Departments of Health and Education for this to occur.

In addition, maternal health and risks are considered. Mothers with acute illness, or possibly severe psychosocial problems such as clinical depression, were referred for treatment. If mothers were still drinking, the risks were discussion with them, and they were encouraged to stop risky drinking, and to consider the option of contraception if appropriate. In the case of significant concerns about a pattern of drinking suggesting dependence or an alcohol use disorder, participants were referred to the local branch of the South African National Council on Alcoholism and Drug Dependence for further intervention.

The pre-post experimental study worked with young infants. Assistance was offered in accessing government welfare grants, where applicable. The study team also provided some developmental support for children through, for example, creating a toy library and play group, aimed at promoting early childhood development and maternal bonding. Malnourished children were referred to a dietician and enrolled into a local protein-energy malnutrition program.

The cross-site questionnaire survey revealed the problems created by the changing manner in which some data was collected, reducing the range of variables that could be meaningfully assessed. For example it was not possible to make comparisons of changes in smoking prevalence over time, or of stress during pregnancy. As far as possible, there is a practical need to create and retain a standard dataset between FAS survey sites, at least for core variables, in order to facilitate such studies in future. This perhaps also has an ethical dimension, in that there is a duty for researchers to optimally use data, especially if there is potential public benefit.

3.6.3 Ethics: Consent and confidentiality

Informed consent was obtained from a parent or guardian for all participating children. For the prevalence surveys, consent forms were sent from schools to parents. A home visit was conducted if parents did not respond to a second reminder, to ensure that learners whose parents were illiterate were not excluded from the study.

Confidentiality of a FAS diagnosis is a key issue given that it may potentially stigmatise the child [256], the mother and other family members. In the consent process for the study, the parent or guardian was specifically made aware that detection of FAS in the child was a significant component of the study. Nevertheless the great majority of parents gave consent to participate, for example in the Kimberley study consent was received for 1510/1587 (95%) of eligible participants.

Confidentiality of records was maintained by appropriate training of staff, storing records in a locked room, and ensuring that electronic records were password protected.

For the prevalence surveys, the diagnosis was fed back to the mother or guardian. The father was included if the couple was together, or the mother gave consent. It was also considered that there is educational benefit for the school principal and teacher to be made aware of a disability or FAS diagnosis. At the time that the diagnosis was fed back to the mother or guardian, the option of sharing the result with the school was discussed and specific consent obtained. Again, the great majority of women consented to sharing of the diagnosis.

3.6.4 Ethics: community and population level issues

Community confidentiality is also an important issue for consideration. Disclosure of study sites may raise community level concerns for example regarding stigmatisation. However, it may be practically difficult to accurately describe a community without giving away the identity of the community. In addition, communities or community leaders may see potential value in the problem being highlighted in their community, to increase awareness and to obtain

resources to tackle the problem. This was the case in the De Aar and Kimberley studies.

The Aurora study was unique in that the request for the study emanated directly from a community member and was supported by the community leaders. At a community meeting the request was expressed that the FAS problem be highlighted and published by name. In this way they hoped to garner attention for the health problems of a community that they felt had been forgotten.

The concerns around identification of study communities can be extended further to the level of the population group. In a local context the possible association of FAS with ethnicity may be relevant for at least four reasons, which may have positive or negative implications. These include fostering appropriate research regarding the risk factors for FAS, appropriate use of public health resources, accurate clinical diagnosis, and avoidance of inappropriate community stereotyping.

If ethnicity has a real association with FAS, it may give important information about causal factors, including historical, cultural, environmental and potential genetic contributions to susceptibility [206]. It may also be important in targeting scarce resources at a public health level. Given for example that the South Africa population is only 9% SAC and approximately 79% BSA [242], choices on whether to target resources in a more focused or more general manner would have big financial implications.

There are also risks. For example, a higher index of suspicion for finding alcohol use or FAS in one community than another may lead to accurate or perhaps over-diagnosis in individuals from the community perceived to be at high risk, but under-diagnosis in the one deemed to be at low risk [93,257].

There is a related risk of more general stereotyping. Adhikari [258] argues that racial stereotyping of Coloured (SAC) identity is deeply ingrained in South Africa, and draws on prejudices against both racial hybridity and Khoisan ancestry. Research in the USA has shown that stereotyping fosters biased behaviour toward minority groups, which may itself create anxiety and promote alcohol and other drug abuse [259].

In South Africa, ethnicity may also be contentious because of conflation with 'race' or population group, the use of which is contentious given the colonial and apartheid history of the country, and because 'race' has no sound scientific basis. Nevertheless, South Africa also officially recognised that redress requires ongoing use of population group labels to facilitate affirmative action and black economic empowerment, and the census thus continues to use apartheid-era racial categories [242].

In the text, and in study 2 which explored the link between FAS and ethnicity, we were conscious of the above complexities, and we attempted to take seriously the injunction of Ellison and de Wet [260] that "the continued use of 'racial' categorisation in health research might be inevitable, particularly for examining the impact of social forces, such as apartheid, and other forms of racism, that use 'racial' categories to create unequal access to health and health care. However, any studies that use 'racial' categories should be careful to avoid legitimising the biological concept of 'race', misidentifying the causes of 'racial' disparities in health and reinforcing 'racial' prejudice."

3.7 DISSEMINATION OF RESULTS

The thesis is based on the following articles published in international peer-reviewed journals. The results section comprises studies 1-5, whereas articles 6 and 7 give supportive information about neurodevelopmental outcomes and are included in the Annexures.

Study 1:

Urban M, Chersich MF, Fourie L, Chetty C, Olivier L, Rosenthal J, Viljoen D. Fetal alcohol syndrome among grade-one children in the Northern Cape Province: prevalence and risk factors. *South African Medical Journal* 2008; 11: 877-882. PMID: 19177895

Journal impact factor: 1.038; cited 79 times (Google scholar)

Associated conference presentation: Urban MF, Chersich MF, Fourie L, Chetty C, Olivier L, Rosenthal J, Viljoen DL. Fetal alcohol syndrome among grade-one children in the Northern Cape province of South Africa: prevalence and risk factors. Poster Presentation, European Human Genetics Conference, Barcelona 2008.

Study 2:

Urban MF, Olivier L, Viljoen D, Lombard C, Louw JG, Drotsky L-M, Temmerman M, Chersich MF. Prevalence of fetal alcohol syndrome in a South African city with a predominantly Black African population. *Alcohol: Clinical and Experimental Research 2015; 39(6):1016-26*. PMID: 25941030

Journal impact factor: 2.829; Cited 13 times (Google scholar)

Associated conference presentation: **Urban MF**, Olivier L, Viljoen D, Temmerman M, Cherisch MF. New evidence on the epidemiology of fetal alcohol syndrome in South Africa. Oral presentation, Southern African Society of Human Genetics conference, Johannesburg, October 2013.

Study 3:

Olivier L*, **Urban M***, Chersich MF, Temmerman M, Viljoen D. Burden of fetal alcohol spectrum disorders in the rural West Coast of South Africa. *South African Medical Journal 2013; 103(6): 402-405.*DOI:10.7196/SAMJ.6249. PMID: 23725961 (*Equal first author)

Journal impact factor: 1.712; Cited 21 times (Google scholar)

Study 4:

Urban MF, Olivier L, Louw JG, Lombard C, Viljoen DL, Scorgie F, Chersich MF. Changes in drinking patterns during and after pregnancy among mothers of children with fetal alcohol syndrome: A study in three districts of South Africa. Drug Alcohol Depend. 2016 Nov 1;168:13-21. doi: 10.1016/j.drugalcdep.2016.08.629.

Journal impact factor: 3.349; Not yet cited on google scholar

Associated conference presentation: **Urban MF**, Olivier L, Viljoen DL, Lombard C, Louw JG, Drotsky L-M, Chersich MF. Ongoing drinking and recurrence risk in South African mothers of children with fetal alcohol syndrome. Poster presentation, 14th World Congress in Fetal Medicine, Crete, June 2015.

Study 5:

Chersich MF, **Urban M**, Olivier L, Davies L, Chetty C, Viljoen D. Universal prevention is associated with lower prevalence of fetal alcohol spectrum disorder in Northern Cape, South Africa: a multicentre before-after study. *Alcohol and Alcoholism*, 2012; 47(1):67-74. PMID: 22037537

Journal impact factor: 1.956; Cited 24 times (Google scholar)

Associated conference presentation: Olivier L, **Urban M**, Cherisch M, Viljoen D. Holistic interventions are effective in reducing the prevalence of FASD in the Northern Cape Province of South Africa: A multi-centre, before-after study. Poster presentation, 33rd Annual meeting of the Research of Society on Alcoholism, June 2010, San Antonio, USA.

Study 6: (Annexure 1)

Davies L, Dunn M, Chersich M, **Urban M**, Chetty C, Olivier L, Viljoen D. Developmental Delay of Infants and Young Children with and without fetal alcohol spectrum disorder in the Northern Cape Province, South Africa. *African Journal of Psychiatry* 2011; *14: 299-305.*

Study 7: (Annexure 2)

Davies L-A, Cockcroft K, Olinger L, Chersich M, **Urban M**, Chetty-Makkan CM, Turnbull OH, Olivier L, Viljoen D. Alcohol exposure during pregnancy alters childhood developmental trajectories in a rural South African community. *Acta Paediatrica*, epub ahead of print, July 2017. DOI:10.1111/apa.13978

CHAPTER 4: RESULTS

The results section is divided into three parts:

- First the prevalence of FAS is described from a range of study sites in the Northern and Western Cape provinces (studies 1-3). It should be noted that related findings are presented in study 4, as well in two studies of longitudinal neurodevelopment (studies 6 and 7 in the Annexures).
- Second, the maternal risk factors are described across three sites, together with implications for prevention (study 4).
- Lastly, a study of a preventive intervention is presented (study 5).

4.1 PREVALENCE OF FAS IN THE NORTHERN AND WESTERN CAPE PROVINCES OF SOUTH AFRICA

4.1.1 STUDY 1

Urban M, Chersich MF, Fourie L, Chetty C, Olivier L, Rosenthal J, Viljoen D. Fetal alcohol syndrome among grade-one children in the Northern Cape Province: prevalence and risk factors. *South African Medical Journal 2008; 98: 877-882* PMID: 19177895

Fetal alcohol syndrome among Grade 1 schoolchildren in Northern Cape Province: Prevalence and risk factors

Michael Urban, Matthew F Chersich, Leigh-Anne Fourie, Candice Chetty, Leana Olivier, Denis Viljoen

Objective. To describe the prevalence, characteristics and risk factors for fetal alcohol syndrome (FAS) and partial FAS among schoolgoing children in Grade 1 in Northern Cape Province, South Africa.

Design. A cross-sectional study using a two-tiered method for ascertainment of FAS/partial FAS cases, comprising: screening of growth parameters, diagnostic assessment for screen-positive children using clinical and neurocognitive assessments, and maternal history of drinking during pregnancy. Mothers or caregivers of FAS children and matched controls were interviewed.

Setting. Primary schools in De Aar (8) and Upington (15).

Subjects. Grade 1 pupils in 2001 (De Aar, *N*=536) and 2002 (Upington, *N*=1 299).

Outcome measures. FAS or partial FAS.

Results. The prevalence of FAS/partial FAS was high: 64/536 (119.4/1 000, 95% CI 93.2 - 149.9) in De Aar, and 97/1 299 (74.7/1 000, 95% CI 61.0 - 90.3) in Upington. Overall, 67.2 per 1 000 children (95% CI 56.2 - 79.7) had full FAS features. Growth retardation was also common in this population: 66.6% (1 181/1 774) were underweight, 48.3% (858/1 776) stunted, and 15.1% had a head circumference <2 SD for age. Mothers of children with FAS were less likely to have full-time employment or have attended secondary school and had lower body mass index, and about 80% currently smoked. Over two-thirds of all pregnancies had been unplanned.

Conclusions. A very high proportion of pupils (nearly 1 in 10) had FAS/partial FAS, the rate in De Aar being the highest yet described in South Africa. FAS/partial FAS may contribute to the extremely high rate of growth retardation in South Africa as a whole and is a major cause of learning disability. These epidemiological features are important in designing preventive interventions.

S Afr Med J 2008; 98: 877-882.

Fetal alcohol syndrome (FAS) was described as an entity in 1973.[1] It is the severe end of a spectrum of deleterious effects caused by prenatal exposure to alcohol, including some or all of the following features: facial dysmorphism, prenatal and/or postnatal growth retardation, and neurological, cognitive and behavioural abnormalities. The term 'fetal alcohol spectrum disorder' describes the effects that can occur in an individual who is prenatally exposed to alcohol, encompassing FAS, partial FAS (PFAS) and other adverse outcomes.[2] Our study focuses on FAS and PFAS because dysmorphic features make them more specific and recognisable diagnoses.

FAS/PFAS is among the most common causes of learning disability worldwide, but especially high rates have been described in parts of South Africa. Whereas the average prevalence of FAS in high-income countries has been estimated at 0.97/1 000,[3] rates reported from Wellington, Western Cape Province, have ranged between 40.5 and 54 per 1 000.[4,5]

The reasons for South Africa's high FAS burden are incompletely understood, and relate to risky maternal alcohol consumption and other maternal personal, social and perhaps genetic factors that increase the risk of FAS. The answers are necessarily multifaceted. Regular binge-drinking (heavy episodic drinking of 5 or more units of alcohol per occasion) is the most risky drinking pattern for FAS.[6] High rates of binge-drinking were found among women attending antenatal clinics in the Western Cape.[7] The *dop* system (alcohol forming part of labourers' wages on wine farms) is believed to have played a role in entrenching binge-drinking.

Maternal factors also linked to increased risk of having a child with FAS include: older age at pregnancy, smoking and low socio-economic status;[3,5,8-10] the latter may be a blanket term for numerous poorly defined factors including psychological depression, unintended pregnancies and poor nutrition that provoke, or interact with, alcohol consumption to exacerbate the effects of high-risk drinking patterns.

We aimed to describe and investigate the prevalence of and risk factors for FAS and PFAS in Grade 1 children in De Aar and Upington, two large towns in Northern Cape Province.

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Methods

The study took place from 2001 to 2004, using the identical methods in De Aar and Upington. Upington is a centre of the viticulture industry on the banks of the Orange River. De Aar is in a sheep-farming area in the Upper Karoo region. Eight schools in De Aar and 15 in Upington participated. Permission for the study was obtained from the Northern Cape Department of Education. All Grade 1 pupils at these schools in 2001 (in De Aar) and in 2002 (in Upington) were enrolled if parents or legal guardians consented. Since primary school attendance is compulsory, it was anticipated that most children in the community would be reached. The study was approved by the University of the Witwatersrand Committee for Research on Human Subjects (M00/11/14).

The prevalence of FAS was determined by active case ascertainment using a two-tier screening method:[4] an initial screening stage followed by a comprehensive diagnostic stage (clinical evaluation, neurocognitive assessment and maternal interview). Identified FAS or PFAS cases were matched with controls.

Stage one: screening

Study nurses obtained anthropometric measurements. Using standard methods, height, weight and head circumference (HC) were measured. Children who were ≤10th percentile of the National Center for Health Statistics charts for height and weight, or alternatively ≤10th centile for HC, were recorded as screen-positive and invited for clinical assessment. This method is very sensitive, although not very specific, for FAS/PFAS.[4]

Stage two: diagnostic evaluation

Screen-positive children were assessed by two experienced dysmorphologists for clinical features of FAS including: history of birth events, developmental milestones and medical problems (obtained from the caregiver and the road-to-health card). Pregnancy history was not included, to ensure that the investigators remained blinded to the history of alcohol consumption. Children were also examined for dysmorphic features, neurological signs and intercurrent illness. To standardise the assessment of dysmorphic features, a checklist was used that yielded a 'dysmorphology score', with a maximum of 35.

The Institute of Medicine (IOM) criteria[11] were used to diagnose FAS and PFAS. Diagnosis of facial features was based on 'gestalt' appearance and included a smooth upper lip and narrow upper vermilion border, and short palpebral fissures on measurement (≤10th centile for age). Positive evidence of neurological abnormality required an HC ≤10th centile, the presence of 'hard' signs on neurological examination, or significant abnormalities on neurocognitive assessment (below 'average range' score in more than 4 of 10 tests).

A diagnosis of FAS required two of the three primary facial features, together with growth retardation and neurological abnormalities. A PFAS diagnosis required at least two of the three FAS facial features and one of growth retardation, neurological abnormality or abnormal neurocognitive assessment. The clinical diagnosis of FAS, but not PFAS, is considered distinctive even in the absence of a history of maternal alcohol consumption in pregnancy.

Children were classified on the clinical assessment into: **FAS** if they fulfilled the IOM criteria as determined by both clinicians; **deferred** if they were uncertain or there was a discrepancy between their diagnoses; or **not FAS** if there were no clinical features of FAS/PFAS. A dysmorphic syndrome other than FAS was considered in children with dysmorphic features.

For each child classified as FAS or deferred, one control was selected from the not FAS group and matched for child's age, sex and ethnicity. Child development and possible maternal risk factors for FAS were compared between cases and controls.

Trained interviewers completed a structured questionnaire with mothers of children in the FAS, deferred or control groups. A shorter proxy interview was used with a guardian if the mother was deceased or untraceable. Interviews obtained data on demographics, socio-economic status, alcohol consumption and other risk factors for having a child with FAS/PFAS. History of alcohol consumption was elicited using a timeline follow-back method.[13]

Children in the FAS, deferred and control groups received a neurocognitive assessment, conducted by a registered psychometrist blinded to the clinical diagnosis; this comprised 10 subtests, each assessing a neurocognitive domain (Table I). All subtests had been validated in South Africa except for Test for Reception of Grammar and DAP Goodenough-Harris, for which raw scores were standardised by converting the raw score to a z score and then comparing each child's z score to the average standard score. South African normative ranges exist for Raven's Coloured Progressive Matrices, but its raw scores were also converted into a standard score since participants did not fall within available age ranges.

A case conference made a final diagnosis; the final diagnostic categories were FAS, PFAS and FAS-negative.

Children identified as having FAS/PFAS were referred to local professionals and other services, including speech and hearing therapists, occupational therapists and physiotherapists. With parental permission, school personnel were informed of each child's diagnosis to facilitate educational support, remedial assessment and follow-up by the Department of Education. Children with other medical conditions were linked with local and regional medical services, as required.

Statistical analysis

Intercooled Stata 8.0 (Stata Corporation, College Station, Texas, USA) was used for statistical analysis. For analysis of categorical variables, the chi-square test was used; for

Table I. Neurocognitive functioning of children with FAS/PFAS and controls

Domain and subtest	Controls	FAS/PFAS*	*p*
Non-verbal reasoning – Raven's Coloured Progressive Matrices (standard)			
N	84	142	
Median (IQR)	0.3 (–0.3 - 0.97)	–0.3 (–0.9 - 0.32)	<0.001
Grammatical contrasts and language comprehension – test for reception of grammar (standard)			
N	85	142	
Median (IQR)	0.1 (–0.45 - 1.02)	–0.5 (–1.0 - 0.14)	<0.001
Visual motor abilities – visual motor integration (standard)			
N	135	132	
Median (IQR)	87 (80 - 95)	77 (69 - 84)	<0.001
Motor co-ordination (standard)			
N	135	132	
Median (IQR)	90 (84 - 95)	84 (75 - 89)	<0.001
Ability to perceive visual information – visual perception (standard)			
N	129	113	
Median (IQR)	75 (65 - 87)	60 (49 - 73)	<0.001
Auditory perception, concepts belonging together and verbal comprehension – word association/similarities (standard)			
N	125	142	
Median (IQR)	7 (4 - 9)	5 (3 - 7)	0.002
Visual perception and cognitive evaluation of stimuli – absurdities/missing parts (standard)			
N	137	145	
Median (IQR)	4 (2 - 6)	2 (1 - 4)	<0.001
Short-term memory and attention – story memory (standard)			
N	139	145	
Median (IQR)	4 (2 - 6)	2 (0 - 5)	0.002
Short-term memory and information encoding – digit span (standard)			
N	139	145	
Median (IQR)	6 (3 - 8)	3 (0 - 4)	<0.001
Estimated intellectual development – DAP Goodenough-Harris (standard)			
N	99	142	
Median (IQR)	0.47 (–0.2 - 1.3)	–0.37 (–1.05 - –0.4)	<0.001

*Includes 38 children with PFAS.
IQR = interquartile range.

continuous variables, we used an unpaired Student's *t*-test or Mann-Whitney *U*-test for normally and non-normally distributed data, respectively. Mantel-Haenszel techniques were used for analysis of categorical data from matched cases and controls; only discordant pairs contributed to this analysis.

Results

Characteristics of study sample

A total of 1 830 pupils were screened in stage 1. In De Aar and Upington, a high proportion of the study population had growth retardation: 66.6% (1 181/1 774) were underweight (<80% of expected weight-for-age); 48.3% (858/1 776) were stunted (<90% of expected height-for-age); and 42.7% (755/1 768) were of low weight-for-height (<80% of expected weight-for-height). As a result, many subjects were screen-positive for FAS/PFAS: more in De Aar (66.4%; 354/533) than Upington (57.4%; 744/1 297; $p<0.001$) (Table II). Differences in denominator are due to missing information.

Prevalence of fetal alcohol spectrum disorders

A total of 123 children were diagnosed with FAS and 38 with PFAS, yielding a FAS prevalence of 67.2/1 000 (95% CI 56.2 - 79.7) and a PFAS prevalence of 20.8/1 000 (95% CI 14.7 - 28.4). The overall rate of FAS/PFAS in De Aar was 64/536 (119.4/1 000, 95% CI 93.2 - 149.9) and in Upington 97/1 299 (74.7/1 000, 95% CI 61.0 - 90.3). Children in De Aar were 1.7 times more likely to have FAS/PFAS than children in Upington (95% CI for OR (odds ratio) 1.2 - 2.4; $p=0.002$).

Children with FAS/PFAS were a mean 4.6 months older than non-FAS children (95% CI 3.3 - 5.9 months; $p<0.001$) which may be due to children repeating Grade 1 because of poor performance or delayed school entry. Since the standard school starting age is the year in which a child turns 7, the FAS/PFAS rate was assessed for children who were <7 years when the year began (i.e. children of standard school-entry age). The FAS/PFAS rate was 10.9/1 000 (51/469) in De Aar and 49/1 000 (53/1 087) in Upington.

No differences were noted in FAS prevalence among ethnic groups: 7.2% (108/1 501) for coloured children versus 5.3% (15/282) for black children (p=0.25). However, in De Aar, coloured children were significantly more likely to have FAS than black children (p=0.007; OR 3.8, 95% CI 1.3 - 10.8). There were insufficient numbers of white children for meaningful comparisons.

Clinical features of children with FAS/PFAS

Growth parameters of FAS/PFAS children were globally abnormal; 98.3% (112/114) were underweight, 89.5% (102/114) stunted, and 86.8% (99/114) low weight-for-height. Mean dysmorphology scores were 12.0 (SD 5.4) for children with FAS, 8.8 (SD 8.8) for children with PFAS, and 3.7 (SD 3.8) for FAS-negative children.

Neurological and neurocognitive results

Microcephaly (HC <2SD for age and sex) was present in 71.9% (82/114) of children with FAS, 44% (16/36) of those with PFAS and 11.0% (180/1 639) of the non-FAS group. Children with FAS/PFAS performed significantly worse than the control children in all 10 neurodevelopmental subtests (Table I).

Interviews

A total of 223 interviews were conducted with mothers (146), grandmothers (37) or other proxies (40) of 95 children with FAS, 29 with PFAS and 99 matched controls. The overall response rate for interviews related to children with FAS/PFAS was 77% (124 of 161 cases).

Differences between mothers of children with FAS/PFAS and control women were noted in socio-demographic characteristics, especially maternal education and employment (Table III). Women with a FAS/PFAS child also had a lower BMI than other women (median 25.9 v. 22.8 kg/m^2; p<0.001).

Discussion

This survey of Grade 1 children found an extremely high prevalence of FAS – higher than that previously reported in Western Cape Province.[4,5,13] Although comparisons of FAS rates can be misleading owing to differences in methodology and diagnostic criteria, we believe that the similar methods we used and the referenced studies in Western Cape Province make them relatively comparable. Rates of FAS reported from South Africa are generally much higher than other countries, where rates of FAS seldom exceed 10/1 000, even in high-risk populations.[14]

These results broaden the evidence that FAS is of considerable public health importance in the Western and Northern Cape provinces, although information available for other provinces of South Africa is limited.

Since mental disability is the most significant effect of FAS, comparing these FAS/PFAS rates to published overall prevalence rates for mental disability due to all causes, is of interest. Worldwide, mental disability rates in developing countries vary from 4 to 138 per 1 000.[15] The fact that FAS/PFAS rates in our study are at the high end of this range indicates the magnitude of the problem.

In South Africa, FAS is often linked to the historical legacy of the *dop* system in wine-farming areas, and stereotypical assumptions are made that FAS is peculiar to the coloured communities that comprised the local workforce. It is noteworthy that the FAS rate is higher in De Aar (a sheep-

Table II. Baseline characteristics of Grade 1 pupils in De Aar and Upington

Variable	Whole study population	De Aar	Upington	p*
Sex				
Female	50.4% (923/1 833)	51.4% (275/535)	49.9% (648/1 298)	
Male	49.7% (910/1 833)	48.6% (260/535)	50.1% (650/1 298)	0.57
Age (yrs) (mean (SD))	7.05 (0.69)	7.04 (0.71)	7.05 (0.68)	0.85
Ethnicity				
Coloured	84.1% (1 537/1 827)	77.7% (414/533)	86.8% (1 123/1 294)	
Black	15.7% (287/1 827)	21.8% (116/533)	13.2% (171/1 294)	
White	0.2% (3/1 827)	0.6% (3/533)	0% (0/1 294)	<0.001
Weight for age (mean z-scores (SD))	-1.20 (1.08)	-1.19 (1.12)	-1.21 (1.07)	0.80
Height for age (mean z-scores (SD))	-1.24 (1.08)	-1.30 (1.18)	-1.21 (1.04)	0.10
Weight for height (mean z-scores (SD))	-0.61 (1.00)	-0.53 (1.03)	-0.64 (0.98)	0.03
Head circumference				
Mean (SD) (cm)	50.7 (2.0)	50.5 (2.1)	50.7 (1.9)	0.05
≤3rd centile	15.5% (278/1 792)	15.6% (83/533)	15.5% (195/1 259)	0.96

*Comparing characteristics of De Aar with Upington (chi-square test for categorical variables and Student's t-test for continuous variables).
SD = standard deviation.

Table III. Results of structured interview with mother or proxy of children with FAS/PFAS and matched controls

	Variable	Controls	FAS/PFAS	p^*
Demographics	Maternal age at time of interview			
	N	74	82	
	Mean years (SD)	35.1 (6.2)	36.1 (6.3)	0.30†
	Marital status of child's mother‡			
	Married	49% (21/43)	23% (12/52)	
	Single or cohabiting	51% (22/43)	77% (40/52)	0.20
	Maternal education			
	No schooling or primary school	40% (27/68)	61% (41/67)	
	Attended secondary school	60% (41/68)	39% (26/67)	0.02
Socio-economic status	Household size: *N*=147; median (IQR)			
	Total members	6 (5 - 7)	6 (4 - 7)	0.65§
	Number of adults	2 (2 - 3.5)	2 (2 - 4)	0.20§
	Number of children	3 (2 - 4)	3 (2 - 5)	0.97§
	Employment status			
	Full-time job	23% (15/66)	8% (6/78)	
	Part-time job or unemployed	77% (51/66)	92% (72/78)	0.01
Family planning	Currently using contraception	73% (48/66)	57% (43/76)	0.56
	Pregnancy of index child			
	Planned	32% (21/66)	17% (13/77)	
	Unintended	68% (45/66)	83% (64/77)	0.16
Tobacco use	Current tobacco use¶	40% (27/67)	79% (63/79)	0.007
	Tobacco used in index pregnancy	49% (23/47)	87% (61/70)	0.03
Alcohol use	Currently drinks alcohol‖	15% (9/61)	66% (49/74)	<0.001
	Alcohol use during index pregnancy	19% (13/70)	82% (80/98)	<0.001
Maternal nutrition	Body mass index (kg/m²): *N*=142; median (IQR)	25.9 (21.5 - 32.7)	22.8 (20.0 - 26.0)	<0.001§

Denominators differ as proxy informants only responded to certain questions.
* Mantel-Haenszel chi-square test, controlled for matching unless noted.
† Student's *t*-test.
‡ Data only available for Upington.
§ Mann-Whitney *U*-test.
¶ Defined as current user if used in last year.
‖ Defined as current user if used in last month.

farming area) than Upington (a wine-farming area), and that there was no overall difference in FAS/PFAS between black and coloured subjects. Therefore, FAS is limited neither to viticultural areas nor to a specific ethnic group.

Maternal drinking during pregnancy was much more frequently reported in mothers of children with FAS/PFAS than in controls. Alcohol consumption was not confirmed in a minority of FAS cases because families could not be traced or proxy interviewees were not always aware of alcohol histories, rather than because a history of alcohol consumption was denied.

The reported rates of drinking in the control and FAS groups remained high across a 7-year interval from the index pregnancy to the time of interview. It is unclear whether stable drinking rates are maintained in alcohol dependency, or the influence of other factors such as social acceptability, which will be important to clarify for identifying appropriate interventions to reduce alcohol consumption.

In this study, children with FAS and PFAS performed poorly across a broad range of neurodevelopmental domains, with significantly lower results than controls in all tests. Markedly lower intellectual functioning and attention deficits were noted during the assessment. Children with FAS/PFAS particularly struggled with language skills – speaking, writing and basic understanding of words. There was a delay in speed and accuracy of problem solving and practically implementing tasks compared with expected developmental age. Neurocognitive deficits were global and not specific to 'executive functioning' as found by some authors.[16]

Small HC is a common clinical feature of FAS, and was used as a screening and diagnostic feature of FAS. The difference in mean HC between the FAS and control groups was therefore not surprising, but the high rate of microcephaly (11%) in children not diagnosed with FAS/PFAS was unexpected. It is unclear whether this represents undetected cases of significant prenatal alcohol exposure (a history of maternal alcohol consumption was only sought in cases and controls)

or is due to other known causes of poor brain growth, such as malnutrition occurring either prenatally (owing to poor placental blood flow) or in early childhood.[17]

There was such a high rate of growth retardation in the study population that we feel that most cases resulted from malnutrition rather than FAS. This resulted in a high false-positive rate for the initial screening test, limiting its usefulness in this population.

The low education levels and employment rates indicate that the study sample is generally of low socio-economic status. The higher rate of FAS/PFAS in women who smoke, are less educated, or lack full-time employment, is consistent with previous reports.[3]

Mothers of FAS/PFAS children had lower BMIs than controls at the time of interview, confirming the findings of a previous small study.[18] The significance is uncertain and may be the result of heavy drinking and/or malnutrition, or be a risk factor for FAS. Further investigation is warranted.

The high rate of unplanned pregnancies and low levels of contraceptive use, especially among mothers of children with FAS, is cause for concern. A previous child with FAS is a strong risk factor for having another child with FAS. Unplanned pregnancy hinders modification of drinking behaviour in early pregnancy, which is important because the first trimester is the period of maximal sensitivity to the embryotoxic effects of alcohol.

Study limitations

The complexities of diagnosing FAS hamper efforts to quantify its burden of disease and institute ongoing FAS surveillance. The most important adverse effects relate to neurodevelopment. Neurocognitive assessments were performed only on children clinically suspected of FAS and matched controls, which may cause under-assessment of fetal alcohol spectrum disorder.

The diagnosis of FAS/PFAS remains clinical, and optimal criteria are under debate,[19,20] with different diagnostic criteria leading to variations in frequency of diagnosis. Our widely used criteria define FAS features less strictly than some other classifications, which may lead to more frequent diagnosis of FAS. Differences in rates of diagnosis of FAS between different classification systems, but similar overall rates of FAS, have been demonstrated.[20]

Although we used a comprehensive battery of neurocognitive subtests, there were shortcomings in the assessment tools. The tests have mostly been validated in South Africa, but the applicability of these tests to children from diverse backgrounds is of concern. Nevertheless, significant differences were found between the FAS/PFAS and the control groups across all domains tested.

The interview response rate was suboptimal as tracing mothers and arranging interviews was more difficult than anticipated, particularly because of the death of a key interviewer. The denominators varied between questions since collateral informants could not answer some questions, and some information was available only for the Upington site.

Generalising our findings to other geographical areas is uncertain as there may be systemic differences between the populations studied and those of other rural or urban areas. The likelihood that our results reflect the burden of FAS in the province is strengthened by the use of two towns in different regions. The unique demographics of the Northern Cape suggest that the results are not generalisable to other parts of South Africa.

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References

1. Jones KL, Smith DW. Recognition of fetal alcohol syndrome in early infancy. *Lancet* 1973; 2: 999-1001.
2. Bertrand J, Floyd RL, Weber MK, *et al. Fetal Alcohol Syndrome: Guidelines for Referral and Diagnosis*. Atlanta, Ga.: Centers for Disease Control and Prevention, 2004: 14.
3. Abel EL, Hannigan JH. Maternal risk factors in fetal alcohol syndrome: provocative and permissive influences. *Neurotoxicol Teratol* 1995; 17(4): 445-462.
4. May PA, Brooke LB, Gossage JP, *et al.* Epidemiology of fetal alcohol syndrome in a South African community in the Western Cape province. *Am J Public Health* 2000; 90(12): 1905-1912.
5. May PA, Gossage JP, Marais AS, *et al.* The epidemiology of fetal alcohol syndrome and partial FAS in a South African community. *Drug Alcohol Depend* 2007; 88: 259-271.
6. Jacobson JL, Jacobson SW, Sokol RJ, Ager JW. Relation of maternal age and pattern of pregnancy drinking to functionally significant cognitive deficit in infancy. *Alcohol Clin Exp Res* 1998; 22(2): 345-351.
7. Croxford J, Viljoen D. Alcohol consumption by pregnant women in the Western Cape. *S Afr Med J* 1999; 99: 962-965.
8. May PA, Gossage JP, Brook LE, *et al.* Maternal risk factors for fetal alcohol syndrome in the Western Cape Province of South Africa: a population-based study. *Am J Public Health* 2005; 95: 1190-1199.
9. Leonardson GR, Loudenberg R. Risk factors for alcohol use during pregnancy in a multistate area. *Neurotoxicol Teratol* 2003; 25: 651-658.
10. May PA, Gossage JP, White-Country M, *et al.* Alcohol consumption and other maternal risk factors for fetal alcohol syndrome among three distinct samples of women before, during, and after pregnancy: the risk is relative. *Am J Med Genet* 2004: 127C: 10-20.
11. Institute of Medicine. Stratton KR, Howe CJ, Battaglia FC, eds. *Fetal Alcohol Syndrome: Diagnosis, Epidemiology, Prevention and Treatment*. Washington, DC: National Academy Press: 1996.
12. Sobell S, Agarwal S, Annis H, *et al.* Cross-cultural evaluation of two drinking assessment instruments: alcohol timeline follow-back and inventory of drinking situations. *Subst Use Misuse* 2001; 36: 313-331.
13. Viljoen DL, Gossage JP, Brooke L, *et al.* Fetal alcohol syndrome epidemiology in a South African community: a second study of a very high prevalence area. *J Stud Alcohol* 2005; 66(5): 593-604.
14. May PA, Gossage J-P. Estimating the frequency of fetal alcohol syndrome, a summary. *Alcohol Res Health* 2001; 25: 159-167.
15. Roeleveld N, Zielhuis GA, Gabreels F. The prevalence of mental retardation: a critical review of recent literature. *Devel Med Child Neurol* 1997; 39: 125-132.
16. Jacobson JL, Jacobson SW. Drinking moderately and pregnancy. Effects on child development. *Alcohol Res Health* 1999; 23(1), 25-30.
17. Ivanovic DM, Leiva BP, Perez HT, *et al.* Head size and intelligence, learning, nutritional status and brain development. *Neuropsychologia* 2004; 42: 1118-1131.
18. Khaole NC, Ramchandani VA, Viljoen DL, Li TK. A pilot study of alcohol exposure and pharmacokinetics in women with or without children with fetal alcohol syndrome. *Alcohol Alcohol* 2004; 39(6): 503-508.
19. Hoyme HE, May PA, Kalberg WO, *et al.* A practical approach to diagnosis of fetal alcohol spectrum disorders: Clarification of the 1996 Institute of Medicine criteria. *Pediatrics* 2005; 115(1): 39-47.
20. Astley SJ. Comparison of the 4-digit diagnostic code and the Hoyme diagnostic guidelines for fetal alcohol spectrum disorders. *Pediatrics* 2006; 118: 1532-1545.

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4.1.2 STUDY 2

Urban MF, Olivier L, Viljoen D, Lombard C, Louw JG, Drotsky L-M, Temmerman M, Chersich MF. Prevalence of fetal alcohol syndrome in a South African city with a predominantly Black African population. *Alcohol: Clinical and Experimental Research 2015; 39(6):1016-1026. PMID:259410030*

Prevalence of Fetal Alcohol Syndrome in a South African City with a Predominantly Black African Population

Michael F. Urban, Leana Olivier, Denis Viljoen, Chanelle Lombard, Jacobus G. Louw, Lian-Marie Drotsky, Marleen Temmerman, and Matthew F. Chersich

Background: Fetal alcohol spectrum disorder (FASD) and fetal alcohol syndrome (FAS) are common in some South African populations, notably those of mixed ancestry descent in rural areas and small towns. Little is known about FAS/FASD prevalence in the majority of South Africans: city dwellers of Black African ethnicity. This study describes the prevalence of FAS in a South African city, comparing 2 suburbs with predominantly mixed ancestry (Roodepan) and Black African (Galeshewe) populations that house over 60% of the city population.

Methods: We conducted a tiered, active case ascertainment study for the prevalence of FAS and also detected some less clinically specific FASD cases. All first-grade learners in the 2 suburbs were eligible for anthropometric screening, and screen-positive learners were assessed for dysmorphic features of FAS. Those with suggestive clinical features received neurocognitive assessment, and maternal or collateral interview. Final diagnosis was made following a case conference.

Results: Complete ascertainment of FAS status was made in 1,503 (94.7%) of 1,587 eligible learners (435 in Roodepan and 1,152 in Galeshewe). Overall, FAS was diagnosed in 83 (5.5%, 95% confidence interval [CI] = 4.4 to 6.8) learners and FASD in 96 (6.4%, 95% CI = 5.2 to 7.7). Levels of FAS were high in both areas: 26 (6.3%, 95% CI = 4.2 to 9.2) learners from Roodepan, compared to 57 (5.2%, 95% CI = 4.0 to 6.7) from Galeshewe ($p = 0.39$). No cases were previously diagnosed. The mortality rate for mothers of FASD children from Galeshewe was 19 of 65 (29%), compared to 3 of 31 (9.7%; $p = 0.03$) for Roodepan. Interviewed mothers in Galeshewe were older and had higher body mass index.

Conclusions: Prevalence of FAS is high in both Galeshewe and Roodepan, and the lack of prior diagnoses indicates that awareness remains low. The maternal mortality rate was especially high in Galeshewe. The unexpectedly high burden of FAS in an urban area with predominantly Black African population mandates extension of surveillance and intervention measures in southern Africa.

Key Words: Fetal Alcohol Syndrome, South Africa, Prevalence, Ethnicity, Alcohol.

FETAL ALCOHOL SYNDROME (FAS) and fetal alcohol spectrum disorder (FASD) more broadly result from the adverse effects of alcohol on the developing fetus and constitute an important cause of developmental disability worldwide (Jonsson et al., 2014). The primary risk factor for FASD is alcohol consumption by pregnant women, especially in a regular and heavy episodic drinking pattern, but multiple environmental cofactors are important and it is more common in women of low socioeconomic status (Abel and Hannigan, 1995; May and Gossage, 2011; May et al., 2013b). Genetic factors may also predispose to FASD (Khaole et al., 2004; Warren and Li, 2005).

Rates of FASD vary between ethnic groups—for example, in the United States, there is an increased risk among Native Americans and Blacks, compared to Whites and Hispanics (Chartier et al., 2013). Ethnicity, however, is a complex concept that encompasses ancestry, national group, birthplace, and language—each of which could have distinct relationships to alcohol-related harm (Cheung, 1993). This makes it difficult to determine whether ethnic variation in FAS prevalence relates to drinking behavior and associated cultural or historical factors, or to environmental and even genetic cofactors. Nonetheless, ethnicity is a commonly used demographic indicator, and it is therefore important to explore the extent to which it serves as a risk factor for FAS in a particular environment.

FAS and FASD occur with very high prevalence in some South African populations (May et al., 2000, 2007, 2013a; Olivier et al., 2013; Urban et al., 2008; Viljoen et al., 2003, 2005), but nationwide data are not available. To date, FAS

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prevalence studies in South Africa have almost exclusively targeted populations with 2 demographic characteristics believed to confer increased risk: (i) residents of rural areas or small towns, and (ii) areas with populations comprising predominantly the mixed ancestry minority group, designated officially as "Coloured." However, the South African population is 79% Black African and only 9% Coloured, and currently over 60% of the population is urbanized due to rapid urbanization in the last 3 decades (Statistics South Africa, 2011). See the Appendix for a fuller description of the "Coloured" and "Black African" population groups in South Africa.

Alcohol abuse is common among adults in South and southern Africa (World Health Organization, 2014), and risky drinking is among the commonest modifiable risk factors for ill health in the region (Lim et al., 2012). Two national surveys found that 15 to 19% of Black African women reported ever drinking alcohol, a rate approximately half that of Coloured women (Department of Health and Medical Research Council, 2007; Parry et al., 2005). Among Black African women, alcohol consumption was higher if they were urbanized, and risky weekend drinking was a common drinking pattern. Morojele and colleagues (2010) also found significant rates of risky drinking among urban Black African women.

The evidence regarding FAS prevalence in city-dwelling and Black African populations of South Africa is limited to a single study in metropolitan Gauteng (Viljoen et al., 2003). This study found 1.9% prevalence of FAS among 830 first-grade learners, with 1.7% prevalence in the subset of 414 learners from 2 predominantly Black African suburbs. The small sample size did not allow for extrapolation to the whole metropole, with over 8 million Black African inhabitants.

The current study, conducted at the request of the Northern Cape provincial government, aimed to describe the prevalence of FAS in an urban center where risky drinking is believed to be common. Two suburbs were selected for the study, with predominantly Coloured and Black African populations, respectively.

MATERIALS AND METHODS

Study Population

The study was conducted at primary schools in the Galeshewe and Roodepan suburbs of Kimberley, the capital city of the sparsely populated Northern Cape Province of South Africa. Kimberley has 236,000 inhabitants and is among the oldest towns in the interior of the country. It developed during the diamond rush of the 1870s and diamond mining has since been the backbone of its economy, which has stagnated in recent decades due to downscaling of mining operations.

Galeshewe developed during the diamond rush and is among the oldest "townships" in South Africa, dating to the 1880s (the term township refers to a high-density suburb set aside for Black South Africans, often in the apartheid era). It has a population of 118,000 people (Sol Plaatjie Municipality, unpublished data) with an ethnic composition of 92% Black African, 7% Coloured, and <1% other; by first spoken language, the composition is as follows: 71% indigenous African languages, 25% Afrikaans, and 3% English (Statistics South Africa, 2012). Most housing is formal and it is relatively well serviced. There is little economic activity in Galeshewe itself, and a high level of unemployment and concomitant social problems including risky drinking and domestic violence (Botes A, Northern Cape Department of Social Development, unpublished data).

Roodepan was established as an area for Coloured people under the Apartheid Group Areas Act in 1975 (B. Nagel, Africana Museum, Kimberley, unpublished data). Although of much more recent origin than Galeshewe, Roodepan is characterized by similar socioeconomic conditions. The population of 27,500 people (Sol Plaatjie Municipality, unpublished data) is predominantly of Coloured ethnicity (83%), with 12% Black African and 5% other. Afrikaans is the first spoken language for 84%, 5% speak indigenous African languages, 9% English, and 2% other (Statistics South Africa, 2012).

Study Participants and Recruitment

The study took place from March 2012 to November 2013 in all 11 primary schools in Galeshewe and all 3 primary schools in Roodepan. All first-grade children were eligible for inclusion.

Study Process

The prevalence of FAS was determined by active case ascertainment, using a tiered screening and diagnostic method that was previously validated and used in South Africa (May et al., 2000; Viljoen et al., 2005). The process includes an initial screening stage (anthropometric measurement), followed by a comprehensive diagnostic stage (clinical evaluation, neurocognitive assessment, and maternal interview) for screen-positive individuals.

Anthropometric Screening

Study nurses obtained anthropometric measurements. Using standard methods, height, weight, and head circumference (HC) were measured. Children who were ≤10th percentile of the Centers for Disease Control and Prevention (CDC) clinical growth charts for height and weight (Centers for Disease Control, 2000), or alternatively ≤10th percentile for HC (using charts of Nellhaus, 1968), were offered clinical assessment.

Clinical Evaluation

Screen-positive children were assessed by an experienced dysmorphologist for dysmorphic features of FAS and neurological signs. To standardize assessment of dysmorphic features, a checklist was used that yielded a "dysmorphology score" with a maximum of 50, which was adapted from that of Hoyme and colleagues (2005). These features included the primary facial features of FAS, namely smooth philtrum of the upper lip, narrow upper vermilion border, and short palpebral fissures (≤10th percentile for age using the chart of Thomas et al., 1987). Positive evidence of neurological abnormality required an HC <3rd percentile or the presence of "hard" signs on neurological examination.

Children with at least 2 of 3 primary facial features of FAS, or neurological abnormality, went on to a full neurocognitive assessment, and an interview was conducted with a parent or guardian.

Neurocognitive Assessment

Neurocognitive assessments were conducted by a psychologist and occupational therapist experienced in developmental assessment. The Griffiths Mental Developmental Scales–Extended

Revised (GMDS-ER) was used to assess neurodevelopment (Griffiths, 1970; Preston, 2006). The GMDS-ER assesses 6 developmental domains from infancy to middle childhood, and the general quotient (GQ) is a composite of the 6 subscale scores, namely locomotor (gross motor skills), personal–social (adaptive functioning), hearing–speech (verbal ability), eye–hand (fine-motor coordination), performance (pattern construction and speed of performance), and practical reasoning (numerical, time, and spatial concepts). Raw scores were converted into z-scores for each subscale as well as for the GQ. The z-scores are considered significantly delayed if they are 2 or more standard deviations below the mean of the GMDS-ER norms (Luiz et al., 2006). For the study, neurodevelopment was considered delayed if the z-score either for the GQ or for at least 2 subscales was significantly delayed.

Maternal Interview

Three community workers, trained as interviewers, completed a structured questionnaire with mothers of children. Interviews obtained data on demographics, socioeconomic status, alcohol consumption, and other risk factors for having a child with FAS/partial FAS. History of alcohol consumption was elicited using a validated timeline follow-back method (Sobell et al., 2001). A shorter "collateral" interview was used with a close family member, or other informant, if the mother was untraceable. This focused on reasons for the mother's unavailability and whether she used alcohol during the index pregnancy.

Final Diagnosis

A final diagnosis was made following a case conference. The final diagnostic categories were "FAS," "partial FAS," "alcohol-related neurodevelopmental deficit" (ARND), "alcohol-related birth defects" (ARBD), or "not FASD." The modified Institute of Medicine criteria (Hoyme et al., 2005) were used to define diagnostic categories. A diagnosis of FAS required at least 2 of the 3 primary facial features, together with growth retardation and either neurological or neurocognitive abnormalities, with or without a history of alcohol use. A diagnosis of partial FAS required at least 2 of the 3 FAS facial features and 1 of growth retardation and neurological or neurocognitive abnormality. In addition, we required a history of alcohol use in pregnancy for this diagnosis to be made. The clinical diagnosis of ARND required a history of alcohol use in pregnancy and otherwise unexplained neurological, cognitive, or behavioral abnormalities. It is important to note that the aim of this tiered study methodology is primarily to detect cases of FAS, and it is expected to miss some cases of partial FAS and most cases of ARND.

Ethics and Health Care

The Premier of the Northern Cape Province requested the study and the provincial Department of Social Development funded it. Approval was obtained from the Departments of Education, Health and Social Development. Informed consent was obtained from a parent or guardian for all participating children. Consent forms were sent from schools to parents. A home visit was conducted if parents did not respond to a second reminder, to ensure that learners whose parents were illiterate were not excluded from the study. IRB approval was granted by the Health Research Ethics Committee of the University of Stellenbosch (approval number N13/01/008).

Permission was obtained from the Department of Health of the Northern Cape Province for children with developmental deficits, health, and social problems to be referred to local professionals and other services, including speech and hearing therapists, occupational therapists and physiotherapists, school psychologists, and healthcare facilities.

With parental permission, school personnel were informed of each child's diagnosis to facilitate educational support, remedial assessment, and follow-up by the Department of Education.

Statistical Analysis

Intercooled Stata 13 (2013) was used for statistical analysis. For analysis of continuous variables, we used an unpaired Student's t-test or Mann–Whitney U-test for normally and non normally distributed data, respectively. The Mantel–Haenszel chi-square or Fisher's exact tests were used for analysis of categorical data. These tests were used to identify differences between the characteristics of children and of mothers of FASD children in Roodepan and in Galeshewe.

RESULTS

Participant Flow and Retention

Complete ascertainment of FAS status, requiring up to 3 visits, was made on 94.7% of children (1,503 of 1,587; Fig. 1). Lack of diagnosis was mostly due to consent not been given (77 of 1,587; 4.9%), with only a further 7 children not completing the study procedures. A total of 113 received full assessment comprising anthropometric measurement, dysmorphology examination, neurodevelopmental assessment, and maternal interview. Stratified by school, ascertainment for FAS status was over 90% for 12 schools and over 85% for the remaining 2 schools (Table 1).

Characteristics of Learners

The mean age of children at the beginning of the school year was 2.4 months higher in Galeshewe than Roodepan ($p < 0.001$) (Table 2). There was a slight excess of males in the whole study population, even higher among the learners with FASD (59 of 93, 61% male). Dysmorphology data pertaining to all children who received dysmorphology assessment, and dysmorphology and neurocognitive data for those with FASD, are also summarized in Table 2. Of learners with FASD, over 90% had a z-score of 2 or more standard deviations below the GMDS-ER norms for the GQ and for the language and practical reasoning domains.

Prevalence of FAS and FASD

A FASD diagnosis was made in 96 children (6.4%) including 83 (5.5%) with FAS, 6 (0.4%) with partial FAS, and 7 (0.5%) with ARND, and none with ARBD (Fig. 1). No differences were detected between the FAS and FASD prevalence in Roodepan and Galeshewe. Twenty-three learners with FASD were repeating first grade: 5 in Roodepan (16% of FASD cases in Roodepan) and 18 (28%) in Galeshewe ($p = 0.30$, Fisher's exact test) (Table 3). We did not have information on whether any non-FASD children were repeating first grade and estimated the rate of FAS and

FASD in new school entrants using the total number of students as denominator.

In learners with FASD, the dysmorphology scores ranged from 10 to 28 of 50 (median = 16), and the GMDS assessments were that 88 (94%) were severely delayed for GQ, with 6 (6%) being less severely delayed.

Characteristics of Mothers of FASD Children

Interview data were obtained from mothers of learners with FASD ($n = 52$), or collateral informants ($n = 42$) (Table 4). In most cases, the collateral informant was a family member, although 2 interviews were with a social worker. The reasons for requiring a collateral informant were as follows: 22 (23%) mothers were deceased, 9 (10%) had abandoned the child, 6 (6%) learners had been removed by social services, and 7 (7%) for other reasons, such as the mother working or studying elsewhere.

Women in Galeshewe were much more likely to use an indigenous African language at home and to report their ethnicity as Black African. Most women were currently unemployed (Table 4) and, of 51 respondents, 22 (43%) gave their occupation as long-term unemployed, 16 (31%) as domestic workers,

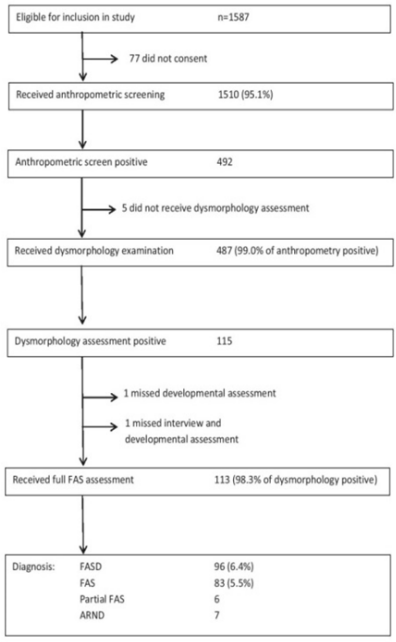

Fig. 1. Participant flowchart.

Table 1. Prevalence of Fetal Alcohol Syndrome and Fetal Alcohol Spectrum Disorder Per School

School (R = Roodepan G = Galeshewe)	*N* Grade 1 pupils	*N* classes (mean class size)	*N* Screened (%)	*N* with study end point	Age Mean (SD)	Fetal alcohol syndrome (FAS) prevalence (as % of screened)	Fetal alcohol spectrum disorder (FASD) prevalence (as % of screened)
R1	191	5 (38)	185 (97%)	185 (97%)	6.21 (0.55)	9 (4.9%)	13 (7.0%)
R2	103	3 (34)	89 (86%)	88 (85%)	6.17 (0.60)	7 (8.0%)	8 (9.1%)
R3	141	4 (35)	137 (97%)	137 (97%)	6.18 (0.58)	10 (7.3%)	10 (7.3%)
Roodepan subtotal	435	12 (36.3)	411 (94.5%)	410 (94.3%)		26 (6.3%)	31 (7.6%)
						95% CI = 4.2 to 9.2	95% CI = 5.2 to 10.6
G1	194	6 (32)	181 (93%)	180 (93%)	6.32 (0.65)	8 (4.4%)	12 (6.6%)
G2	96	3 (32)	95 (99%)	95 (99%)	6.05 (0.50)	0 (0%)	0 (0%)
G3	129	3 (43)	125 (97%)	125 (97%)	6.27 (0.53)	2 (1.6%)	2 (1.6%)
G4	53	2 (27)	53 (100%)	53 (100%)	6.20 (0.65)	3 (5.7%)	4 (7.5%)
G5	81	3 (27)	73 (90%)	69 (85%)	6.60 (0.75)	3 (4.1%)	3 (4.1%)
G6	35	1 (35)	33 (94%)	33 (94%)	6.40 (0.65)	1 (3.0%)	2 (6.1%)
G7	98	3 (33)	93 (95%)	92 (94%)	6.58 (0.57)	11 (11.8%)	13 (14.0%)
G8	103	4 (26)	95 (92%)	95 (92%)	6.61 (0.64)	7 (7.4%)	7 (7.4%)
G9	178	5 (36)	174 (98%)	174 (98%)	6.65 (0.45)	9 (5.2%)	9 (5.2%)
G10	132	4 (33)	129 (98%)	129 (98%)	6.24 (0.65)	12 (9.3%)	12 (9.3%)
G11	53	2 (27)	48 (91%)	48 (91%)	6.16 (0.45)	1 (2.1%)	1 (2.1%)
Galeshewe subtotal	1,152	36 (32.0)	1,099 (95.4%)	1,093 (94.9%)		57 (5.2%)	65 (5.9%)
						95% CI = 4.0 to 6.7	95% CI = 4.6 to 7.5
Total	1,587	48 (33.1)	1,510 (95.1%)	1,503 (94.7%)		83 (5.5%)	96 (6.4%)
						95% CI = 4.4 to 6.8	95% CI = 5.2 to 7.7

Table 2. Characteristics of Learners Screened for Fetal Alcohol Syndrome in 2 Suburbs of Kimberley

	Both suburbs	Roodepan	Galeshewe	*p*
Descriptive data in all learners	*n* = 1,510	*n* = 411	*n* = 1,099	
Sex (% female)	715 (47.4%)	195 (47.4%)	520 (47.3%)	0.96*
Mean age[a] (SD)	6.34 years (0.61)	6.19 (0.57)	6.39 (0.62)	<0.001**
Weight				
Mean (SD)	20.7 kg (3.4)	19.7 kg (3.23)	21.0 kg (3.4)	<0.001**
<5th (percentile (CDC, 2000; Kuczmarski et al., 2002)	182 (11.9%)	74 (18.0%)	108 (9.8%)	<0.001*
Height				
Mean (SD)	116.9 cm (6.0)	115.0 (6.0)	116.9 (6.0)	<0.001**
<5th (percentile (CDC, 2000)	160 (10.6%)	61/411 (14.8%)	99/1,099 (9.0%)	0.001*
Head circumference				
Mean (SD)	51.5 cm (1.7)	51.4 cm (1.8)	51.6 cm (1.6)	0.06**
<3rd percentile[b]	114 (7.5%)	43 (10.5%)	71 (6.4%)	0.009*
BMI (kg/m^2)				
Mean (SD) in females	*n* = 715 14.9 (1.8)	*n* = 195 14.7 (1.8)	*n* = 520 15.1 (1.8)	0.008**
Mean (SD) in males	*n* = 795 15.1 (1.6)	*n* = 216 14.9 (1.6)	*n* = 579 15.2 (1.6)	0.02**
Dysmorphology assessment data	*n* = 487	*n* = 141	*n* = 346	
Palpebral fissure length				
Mean (SD)	24.3 mm (1.8)	23.4 mm (2.3)	24.6 mm (2.1)	<0.001**
≤10th percentile	176 (36.1)%	68 (48.2)%	108 (31.2)%	<0.001*
Clarren score philtrum of 4 to 5/5	128 (27.1%)	28 (20.6%)	100 (29.8%)	0.03*
Clarren score vermilion of 4 to 5/5	38 (8.0%)	21 (15.4%)	17 (5.1%)	<0.001*
Dysmorphology score				
Mean (SD)	9.8 (4.8)	10.5 (5.1)	9.5 (4.7)	<0.001**
Dysmorphology data in learners with FASD	*n* = 96	*n* = 31	*n* = 65	
Palpebral fissure length				
Mean (SD)	22.8 mm (2.0)	21.9 mm (1.4)	23.3 mm (2.1)	0.001**
≤10th percentile	75 (78%)	27 (87%)	48 (74%)	0.14*
Clarren score philtrum of 4 to 5/5	90 (94%)	27 (87%)	63 (97%)	0.06*
Clarren score vermilion of 4 to 5/5	32 (33%)	15 (48%)	17 (26%)	0.03*
Dysmorphology score	*n* = 96	*n* = 31	*n* = 65	
Mean (SD)	16.6 (3.6)	17.3 (3.8)	16.3 (3.5)	0.23**
z-Scores for GMDS-ER in learners with FASD	*n* = 96	*n* = 31	*n* = 65	
General quotient (GQ)				
>−1.0	2 (2%)	2 (6%)	0 (0%)	0.10***
−1.0 to −1.9	5 (5%)	2 (6%)	3 (5%)	
≤−2.0	89 (93%)	27 (87%)	62 (95%)	
Locomotor				
>−1.0	64 (67%)	23 (74%)	41 (63%)	0.27***
−1.0 to −1.9	28 (29%)	6 (19%)	22 (34%)	
≤−2.0	4 (3%)	2 (6%)	2 (3%)	
Personal-social				
>−1.0	23 (24%)	10 (32%)	13 (20%)	0.14***
−1.0 to −1.9	39 (41%)	14 (45%)	25 (38%)	
≤−2.0	34 (35%)	7 (23%)	27 (42%)	
Language				
>−1.0	1 (1%)	0 (0%)	1 (2%)	0.69***
−1.0 to −1.9	2 (2%)	1 (3%)	1 (2%)	
≤−2.0	93 (97%)	30 (97%)	63 (97%)	
Eye-hand				
>−1.0	5 (5%)	4 (13%)	1 (2%)	0.08***
−1.0 to −1.9	23 (24%)	7 (23%)	16 (25%)	
≤−2.0	68 (71%)	20 (65%)	48 (74%)	
Performance				
>−1.0	42 (43%)	14 (45%)	28 (43%)	0.82***
−1.0 to −1.9	26 (27%)	7 (23%)	19 (29%)	
≤−2.0	28 (29%)	10 (32%)	18 (28%)	
Practical reasoning				
>−1.0	0 (0%)	0 (0%)	0 (0%)	0.04***
−1.0 to −1.9	5 (5%)	4 (13%)	1 (2%)	
≤−2.0	91 (95%)	27 (87%)	64 (98%)	

SD standard deviation.
*Chi-square test; **unpaired Student's *t*-test; ***Fisher's exact test.
[a]Age at start of school year.
[b]See reference Nellhaus (1968).

Table 3. Prevalence of Fetal Alcohol Syndrome in 2 Suburbs of Kimberley

	Both suburbs (n = 1,503)	Roodepan (n = 410)	Galeshewe (n = 1,093)	p
FASD prevalence	96 (6.4%) 95% CI = 5.2 to 7.7	31 (7.6%) 95% CI = 5.2 to 10.6	65 (5.9%) 95% CI = 4.6 to 7.5	0.25*
FAS prevalence	83 (5.5%) 95% CI = 4.4 to 6.8	26 (6.3%) 95% CI = 4.2 to 9.2	57 (5.2%) 95% CI = 4.0 to 6.7	0.39*
"Minimum" FASD prevalence[a]	73 (4.9%) 95% CI = 3.8 to 6.1	26 (6.3%) 95% CI = 4.2 to 9.2	47 (4.3%) 95% CI = 3.2 to 5.7	0.10*
"Minimum" FAS prevalence[a]	65 (4.3%) 95% CI = 3.4 to 5.5	23 (5.6%) 95% CI = 3.6 to 8.3	44 (4.0%) 95% CI = 2.90 to 5.4	0.18*

*Chi-square test.
[a]Excludes FASD-/FAS-affected participants who were repeating grade 1.

9 (18%) blue-collar workers, 2 (4%) office workers, and 2 (4%) other, with no difference between suburbs (p = 0.21).

Maternal Alcohol and Substance Use

A history of drinking in pregnancy was given by 80 (87%) of 92 informants in total and by 45 (90%) of 50 mothers. Information regarding current drinking could only be obtained from mothers: Of 48 maternal respondents, 44 (92%) had consumed alcohol in the preceding 12 months (current drinkers). Of current drinkers, 29 (66%) indicated that they drank more now than in the index pregnancy, and 36 (82%) that they had been drunk at least once in the past year or could not remember how often they had been drunk. The women were primarily weekend drinkers, with only 1 woman reporting daily drinking. The number of standard drinks they reported personally consuming per drinking session were as follows: 3 to 4 drinks in 10 women (23%), 5 to 9 drinks in 14 (32%), over 10 drinks in 10 (23%), and 10 women were uncertain (23%). One (2%) said she received alcohol as part of her salary.

In both Roodepan and Galeshewe, the commonest drink was commercial lager beer (27 of 50 [54%]), followed by cider (10 of 50 [20%]). In Galeshewe, 6 (17%) of 35 mothers drank traditional (sorghum) beer and 3 (9%) drank spirits, whereas in Roodepan, 5 (33%) of 15 drank wine. Women in Galeshewe were less likely to be smokers, and no other substance abuse was reported.

Risk of FASD Recurrence

Mothers reported that 32 (62%) of 52 index pregnancies were unplanned. Of 48 maternal respondents, 25 (52%) were at risk of a further child with FASD, as they currently used alcohol and were either pregnant (3 women; 6%) or sexually active and not using contraception (22 women; 46%). A related point is that none of the interviewees were aware of the index child having FAS/FASD prior to the diagnosis being made in the study.

DISCUSSION

Characteristics of the Study Population of Learners

twb 0.25wThis study focused on 2 low-income suburbs that comprise 62% of the population of one of the secondary cities, and a provincial capital, of South Africa. Consistent with the low-income setting, the rate of growth stunting (height <5th percentile) was high in both suburbs. There was a higher prevalence of low height, weight, and HC for age, and lower mean body mass interval (BMI) in schools with predominantly Coloured scholars. This may relate in part to FASD, but may also indicate other environmental, nutritional, epigenetic, and genetic differences between the communities.

The mean dysmorphology score was significantly higher for learners receiving assessments in Roodepan than Galeshewe, but not when only comparing children with FASD between the 2 sites. It is unclear whether this relates to prenatal alcohol exposure, or for other reasons, such as possible ethnic variation.

There was no significant difference in GQ between learners with FASD in the 2 suburbs. A significant difference was detected for the practical reasoning domain, although this may relate to the more frequent use of interpreters in Galeshewe. The vast majority of learners with FASD were significantly delayed for language and practical reasoning, compared to a minority with significant delay for the locomotor, personal–social, and performance domains. This is consistent with evidence from a prior study on South African children with FAS that the predominant effect is on higher order cognitive function (Adnams et al., 2001).

Prevalence of FAS/FASD

The study found a very high prevalence of FAS/FASD (prevalence above 4% in all but 3 of 14 schools), in both communities. As the study included all learners at all 14 primary schools in the study area, and FAS status was determined for almost 95% of learners, the study demonstrates clearly that FAS/FASD is a significant public health problem in both communities. We noted that a number of learners with FASD were repeating grade 1, thus possibly overestimating the FASD rates per age–cohort entering school. We corrected for this by calculating rates of FASD excluding learners with FASD who were repeating first grade—the reduced estimate for both FASD and FAS prevalence remains above 4% and not significantly different between the 2 communities.

Table 4. Interview Data from Caregivers (Maternal or Collateral) of Learners with Fetal Alcohol Spectrum Disorder

Variable	Categories	Both suburbs	Roodepan	Galeshewe	*p*
Interview type (n = 94)	Maternal	52 (55%)	17 (55%)	35 (56%)	0.95*
	Collateral	42 (45%)	14 (45%)	28 (44%)	
Home language (n = 93)	Afrikaans or English	31 (33%)	30 (100%)[a]	1 (2%)	<0.001*
	Afrikaans and African	5 (54%)	–	5 (8%)	
	African (mainly Setswana)	57 (61%)	–	57 (90%)	
Maternal ethnicity (n = 52)	Black African	30 (58%)	0	30 (86%)	<0.001*
	Coloured	22 (42%)	17 (100%)	5 (14%)	
Maternal age at study start (n = 52)	Mean (SD)	35.4 (6.6)	30.9 (6.6)	37.5 (5.5)	<0.001**
Maternal gravidity (n = 52)	Mean (SD)	3.7 (1.7)	3.7 (1.9)	3.7 (1.6)	0.97**
Maternal height (cm)	n	52	17	35	0.64**
	Median (IQR)	156.0 (150.5 to 160.0)	156 (151.5 to 157)	153 (149 to 160)	
Maternal weight (kg)	n	52	17	35	0.08**
	Median (IQR)	58 (44 to 71)	47 (41 to 60)	63 (45 to 77)	
Maternal BMI (kg/m^2)	n	49	17	35	0.12**
	Median (IQR)	23.6 (18.5 to 30.3)	20.5 (16.6 to 23.6)	26.3 (19.2 to 31.1)	
Highest educational level achieved (n = 52)	Nil	2 (4%)	–	2 (6%)	0.23*
	Primary	15 (29%)	3 (18%)	12 (34%)	
	Secondary	35 (67%)	14 (82%)	21 (60%)	
	Tertiary	–	–	–	
Monthly household income (n = 52)	Median (IQR)	USD189 (84 to 321)	USD300 (150 to 450)	USD171 (84 to 284)	0.03°
Employment (n = 52)	Currently unemployed	38 (73%)	15 (88%)	23 (66%)	0.23*
	Part-time work	8 (15%)	1 (6%)	7 (20%)	
	Fulltime work	6 (12%)	1 (6%)	5 (14%)	
Grant received (n = 52)	Total received grant	49/52 (94%)	16/17 (94%)	33/35 (94%)	0.98*
	Child support	47/52 (90%)	14/17 (82%)	33/35 (94%)	0.17*
	Pension	7/52 (13%)	1/17 (6%)	6/35 (17%)	0.26*
	Disability grant	3/52 (6%)	3/17 (18%)	0/35	0.01*
Housing (n = 52)	Formal urban	33 (63%)	10 (59%)	23 (66%)	0.63*
	Informal urban	19 (37%)	7 (41%)	12 (34%)	
	Farm/rural = nil	–	–	–	
Duration current residence (n = 52)	<5 years	8 (15%)	1 (6%)	7 (20%)	0.14*
	5 to 9.9 years	13 (25%)	4 (24%)	9 (26%)	
	10 to 19.9 years	19 (37%)	5 (29%)	14 (40%)	
	20+ years	12 (23%)	7 (41%)	5 (14%)	
Marital status (n = 52)	Single	28 (54%)	8 (47%)	20 (57%)	0.56*
	Living together	13 (25%)	4 (24%)	9 (26%)	
	Married	11 (21%)	5 (29%)	6 (17%)	
Religious (i.e., observant)		49/52 (94%)	17/17 (100%)	32/35 (91%)	0.21*
Alcohol use in pregnancy	(maternal and collateral interviews)	80/91 (88%)	23/29 (79%)	57/62 (92%)	0.09*
Alcohol use in pregnancy	(maternal interviews only)	45/50 (90%)	12/15 (80%)	33/35 (94%)	0.12*
Alcohol use in past year		44/48 (92%)	12/14 (86%)	32/34 (94%)	0.34*
Drinking pattern (current)	All/most weekends	34/44 (77%)	12/12 (100%)	22/32 (69%)[b]	0.07*
	Once a month	9/44 (20%)	0/12 (0%)	9/32 (28%)	
	Occasional	1/44 (2%)	0/12 (0%)	1/32 (3%)	
Drinking days per weekend (current)	Friday	23/44 (52%)	10/14 (71%)	13/30 (43%)	0.17*
	Saturday	41/44 (93%)	13/14 (93%)	28/30 (93%)	
	Sunday	10/44 (23%)	5/14 (36%)	5/30 (17%)	
	Total drinking days	74/132 (52%)	28/42 (67%)	46/90 (51%)	
Tobacco use in pregnancy		18/49 (37%)	9/16 (56%)	9/33 (27%)	0.05*
Maternal death		22/96 (23%) 95% CI = 16 to 32	3/31 (9.7%), 95% CI = 2.6 to 26	19/65 (29%), 95% CI = 20 to 41	0.03*

*Chi-square.
**Unpaired *t*-test.
°Rank-sum test.
[a]One woman spoke English.
[b]Includes 1 women who drank on most days.

FASD in a City Setting and in Predominantly Black African Suburbs

As the study area includes almost two-thirds of the population of Kimberley, the study provides evidence of a high rate of FAS/FASD within this city as a whole. The findings in Galeshewe are the first conclusive evidence that FAS/FASD is a sizable public health problem in a predominantly Black African community in South Africa.

The only prior study to assess rates of FAS in a South African city (Viljoen et al., 2003) found 16 cases of FAS

(1.9%, 95% CI = 1.2 to 3.1) among 830 learners in 4 selected low-income areas in metropolitan Gauteng, which includes the city of Johannesburg. That study found 7 cases of FAS (1.7%, 95% CI = 0.8 to 3.5) among 414 school entry children from 2 areas with a predominantly Black African population. Although giving preliminary evidence of a possible FAS problem in the metropole, the sample was not large or representative enough to draw firm conclusions. This is particularly true of the subsample from 2 Black African areas.

One other study has reported rates of FAS among children of women who self-identified as Black African (Urban et al., 2008), but in the context of 2 small towns with predominantly Coloured populations. In that environment, a substantial proportion of Black Africans had FAS (5.3% of 282), compared to 7.2% of 1,501 Coloured children.

Generalizability of Findings

The extent to which our findings can be extrapolated to other predominantly Black African communities in South Africa is uncertain. The South African Demographic and Health Survey found heterogeneous levels of alcohol consumption, with greater consumption by urban than rural Black African women, and variation by province (Parry et al., 2005). Areas with known high rates of female alcohol consumption are expected to be high risk, although the existing data give little geographic detail.

The generalizability of our findings in Galeshewe depends on the reasons for high FASD rate. If broad socioeconomic factors such as unemployment and poverty are important, then Galeshewe has many features in common with other townships in South Africa. However, there may be more specific historical factors at play: The record indicates a long history of problem drinking in Kimberley, with "drinking, fighting, beer making, and gambling" already frequent in the early 20th century (Lunderstedt S, unpublished data). In addition, there is evidence to suggest a history of female drinking, for example, municipal beer halls were established in the 1940s, with separate drinking areas for women (Allen V et al., unpublished data).

The long history of Galeshewe as an urban settlement may have allowed for attrition of sociocultural prohibitions on female drinking, similar to descriptions of "acculturation" in other populations (Caetano, 1987; Caetano et al., 2009). Kimberley's mining history may also be contributory, in keeping with evidence that residents of cities with a mining history have higher rates of alcohol and substance use compared to those in other South African cities (Sharp et al., 2014). In addition, more recent economic difficulties due to downscaling of mining activity may be important, because there is good evidence that binge drinking increases during economic downturns—among both unemployed and employed individuals (Dee, 2001).

Variation in FAS Rate Between Schools

The rates of FAS/FASD varied widely between schools, especially in Galeshewe. There was no obvious reason for this, and schools with high rates of FASD were often located nearby schools with low rates. Further investigation is warranted. The heterogeneity of FASD rates has implications for surveillance—if schools are sampled, a sufficient number should be included to ensure representativeness.

Prior Diagnosis of FAS in the Study Population

It is clear that FASD remains very underdiagnosed in this community: None of the cases had been previously diagnosed, even those with pathognomonic clinical features of FAS or who repeated first grade. For this reason, few received a grant to assist with care of a disabled child, although most received the child support grant, which is a small sum available for all children from families with limited financial means. This is consistent with the idea that FASD is an "unseen disability" (Paley, 2009) as a result of limited awareness by the community and professionals, as well as the frequently subtle clinical features (May et al., 2009), and specific measures are required to increase awareness.

Maternal Demographic Characteristics

Many of the previously described social determinants of FASD were prevalent in this study. A high proportion of women were unemployed and a significant minority lived in informal housing. Mothers from Galeshewe were older and had a higher BMI than those from Roodepan, despite lower household income. The reasons are unclear, but the difference in BMI may reflect the low average BMI of South African Coloured mothers of a FASD child, as previously been described by comparison with Plains Indian women from the United States (May et al., 2004).

Maternal Alcohol Consumption Patterns and Risk of FASD Recurrence

The high rate of FASD suggests that traditional patterns of alcohol use have broken down to a significant degree within this Black African community. In keeping with this, sorghum beer (the type of alcohol originally brewed by Black African communities in the precolonial era) was only used by a minority of those studied, whereas commercial lager beer was widely used.

Most surviving mothers continued with risky drinking behaviors and at least half were at risk of another alcohol-exposed pregnancy, in which case the risk of FASD recurrence would exceed 50% (Paintner et al., 2012).

Maternal alcohol consumption was denied in 11 (12%) of 91 cases. In 4 cases (4%), the interviewer had other evidence to indicate that the history was unreliable. It was unclear whether the remaining 7 cases (8%) represented women who

concealed their history of alcohol use, collateral informants who were unaware, or whether there was some misclassification as FASD. Although the numbers in this group were small, there were no differences evident in maternal characteristics compared to other study participants. It has been suggested that stigmatization of female drinking results in under reporting of alcohol use among Black African women (Mphi, 1994; Siegfried et al., 2001), but we found no difference in reporting rates between Black African and Coloured women.

Maternal Mortality Rate

Almost a quarter of mothers to children with FASD had died by the time the child reached first grade. This is higher than the rates of 7 to 18% described in previous FASD prevalence surveys in South African communities (May et al., 2000, 2007; Olivier et al., 2013; Viljoen et al., 2005). The maternal death rate of 29% in Galeshewe was particularly high and above that in Roodepan.

The difference in maternal mortality rates is likely to relate to maternal HIV infection which, together with coinfections such as tuberculosis, is the commonest cause of death in adults in the Northern Cape Province (Statistics South Africa, 2014). There is a high prevalence of HIV among women attending antenatal clinics in the district (18.7% in 2011; Health Systems Trust, 2014), and prevalence in adults is twice as high in Galeshewe as in Roodepan (Northern Cape Province Department of Health, unpublished data). In addition, alcohol consumption, and especially heavy episodic drinking, is a risk factor for contracting HIV (Baliunas et al., 2010) and for poor HIV treatment outcomes (Azar et al., 2010). Violence and injury is also a relatively frequent cause of death in the province, and also potentially alcohol-related, but there is no evidence that this or another cause would account for the difference in mortality rates between the 2 communities.

Strengths and Limitations

Strengths. The study was conducted by a team experienced in FAS surveillance, investigating a large and representative study cohort, and a high proportion of participants reached their study end point.

Limitations. For logistical reasons, a tiered screening and diagnostic process was used, with neurodevelopmental assessments only being conducted on children who screened positive on both anthropometric and dysmorphic features. This method is expected to detect virtually all cases of FAS, but will underestimate the prevalence of partial FAS and especially ARND.

The methodology used did not allow for calculation of FAS rates per ethnic or language group, as these data were not collected for the whole study population. In addition, while each area had a predominant ethnic group, there was some overlap in the self-identified ethnicity of participants in the 2 communities. Nevertheless, the study does show that FAS is present at significant levels in an area with a predominantly Black African population, and in individuals whose mothers self-identified as Black African, and spoke an African language at home.

CONCLUSIONS AND RECOMMENDATIONS

We found a high rate of FAS in a South African city with a predominantly Black African population. This challenges the notion that FAS/FASD is largely a condition of the minority Coloured population of South Africa and demonstrates that FAS is more widespread than previously thought. It remains unclear to what extent the findings are generalizable to other apparently similar environments.

There is a need to further delineate the high-risk groups for FAS and to better define target groups for surveillance and prevention measures. We recommend, in line with Jonsson and colleagues (2014), that surveillance be extended to further urban areas in South and southern Africa. Specific characteristics of this community which may be relevant are that it is a long-established city, with a predominantly mining heritage, and current economic difficulties.

The fact that no cases of FAS had been previously diagnosed suggests a lack of awareness by health professionals in this area and perhaps the community more broadly. Interventions have been shown to reduce both alcohol consumption (Chang, 2004-2005) and rates of FASD (Chersich et al., 2012), and practical implementation of primary, secondary, and tertiary prevention measures is urgently required.

The reasons for the very high mortality rate of mothers in Galeshewe require further investigation, but may relate to co-occurrence with HIV/AIDS.

APPENDIX

The South African Census uses the terms "Black African" to denote the majority population of South Africa and "Coloured" to designate the largest minority population group (although the term "Coloured" remains contested in South Africa, it does not have a necessarily derogatory meaning). The history and ancestral background of these 2 groups differ significantly.

The term "Coloured" refers to a highly admixed population that developed during successive periods of colonization by the Dutch and British (between 1652 and 1910). This population derives from a variety of ancestral sources and is best recorded in the Western Cape Province of South Africa, where the historical record and genomic evidence (De Wit et al., 2010) concur that the major ancestries are Khoisan (the indigenous population of the area into which the Cape Colony encroached), European, Black African (predominantly slaves from East Africa), and Asian (slaves or politi-

cal exiles from South Asia and the Dutch East Indies). This population remained subject to discriminatory colonial laws throughout the colonial period. Over time, this largely Afrikaans-speaking population became identified as "Coloured," and the term was subsequently used as a designation in the apartheid era (1948 to 1990) when, although discriminated against, Coloureds held an intermediate status between White and Black South Africans.

From the early days of the Cape Colony, the development of viticulture ensured that alcohol was readily available. A daily measure of alcohol (or "tot") was given to slaves on the wine farms. After slavery was abolished in 1834, this evolved into the "tot system" that entailed the provision of alcohol as part payment or incentive for farm work. The tot system was widely used on farms in the expanding Cape Colony and continued in modified form until 1990. It is considered important in the entrenchment and spread of risky drinking practices in the Coloured population (Viall et al., 2011).

In contrast, Black Africans originate primarily from several bantu language indigenous tribes that inhabited parts of modern South Africa that were mostly outside the early Cape Colony. They suffered land dispossession from the 1830s and especially in the early 20th century and were subjected to the worst effects of subsequent apartheid, but did not receive large-scale exposure to effects of earlier colonial rule such as slavery and the tot system. Urbanization of Black Africans increased from the late 19th century, was severely curtailed in the apartheid era, and has increased rapidly since.

Black South Africans retain significant elements of their precolonial cultures, such as the use of an indigenous African language. An alcohol-related example is the cultural prohibition on female drinking (Mphi, 1994; Siegfried et al., 2001), the reduction of which may partially explain why the prevalence of risky drinking by urbanized Black African women is higher than those from more traditional rural areas.

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REFERENCES

Abel EL, Hannigan JH (1995) Maternal risk factors in fetal alcohol syndrome: provocative and permissive factors. Neurotoxicol Teratol 17:445–462.

Adnams CM, Kodituwakku PW, Hay A, Molteno CD, Viljoen D, May PA (2001) Patterns of cognitive-motor development in children with fetal alcohol syndrome from a community in South Africa. Alcohol Clin Exp Res 25:557–562.

Azar MM, Springer SA, Meyer JP, Altice FL (2010) A systematic review of the impact of alcohol use disorders on HIV treatment outcomes, adherence to antiretroviral therapy and health care utilization. Drug Alcohol Depend 112:178–193.

Baliunas D, Rehm J, Irving H, Shuper P (2010) Alcohol consumption and risk of incident human immunodeficiency virus infection: a meta-analysis. Int J Public Health 55:159–166.

Caetano R (1987) Acculturation, drinking and social settings among U.S. Hispanics. Drug Alcohol Depend 19:215–226.

Caetano R, Ramisetty-Mikler S, Rodriguez LA (2009) The Hispanic Americans Baseline Alcohol Survey (HABLAS): the association between birthplace, acculturation and alcohol abuse and dependence across Hispanic national groups. Drug Alcohol Depend 99:215–221.

Centers for Disease Control (2000) CDC clinical growth charts. Available at: http://www.cdc.gov/growthcharts/. Accessed September 27, 2014.

Chang G (2004-2005) Screening and brief intervention in prenatal care settings. Alcohol Res Health 28: 80–84.

Chartier KG, Vaeth PA, Caetano R (2013) Focus on: ethnicity and the social and health harms from drinking. Alcohol Res 35:229–237.

Chersich MF, Urban M, Olivier L, Davies LA, Chetty C, Viljoen D (2012) Universal prevention is associated with lower prevalence of fetal alcohol spectrum disorders in Northern Cape, South Africa: a multicentre before-after study. Alcohol Alcohol 47:67–74.

Cheung YW (1993) Approaches to ethnicity: clearing roadblocks in the study of ethnicity and substance use. Int J Addict 28:1209–1226.

Griffiths R (1970) The abilities of young children: a comprehensive system of mental measurement for the first eight years of life (Association for Research in Infant and Child Development). Reprinted by The Test Agency Ltd, Amersham, UK, 1984.

De Wit E, Delport W, Rugumika CE, Meintjies A, Moller M, Van Helden PD, Seoighe C, Hoal EG (2010) Genome-wide analysis of the structure of the South African coloured population in the Western Cape. Hum Genet 128:145–153.

Dee TS (2001) Alcohol abuse and economic conditions: evidence from repeated cross-sections of individual-level data. Health Econ 10:257–270.

Department of Health and Medical Research Council (2007) South Africa Demographic and Health Survey, 2003. Department of Health, Pretoria. Available at: http://www.mrc.ac.za/bod/sadhs.htm. Accessed September 12, 2014.

Health Systems Trust (2014) 2012 National Antenatal Sentinel HIV & Herpes Simplex Type-2 Prevalence Survey. Department of Health, Pretoria. Available at: http://www.hst.org.za/publications/2012-national-antenatal-sentinel-hiv-herpes-simplex-type-2-prevalence-survey. Accessed September 14, 2014.

Hoyme HE, May PA, Kalberg WO, Kodituwakku P, Gossage JP, Trujillo PM, Buckley DG, Miller JH, Aragon AS, Khaole N, Viljoen DL, Jones KL, Robinson LK (2005) A practical clinical approach to diagnosis of fetal alcohol spectrum disorders: clarification of the 1996 Institute of Medicine Criteria. Pediatrics 115:39–47.

Jonsson E, Salmon A, Warren KR (2014) The international charter on the prevention of fetal alcohol spectrum disorder. Lancet Glob Health 2:e135–e137.

Khaole NCO, Ramchandani VA, Viljoen DL, Li T (2004) A pilot study of alcohol exposure and pharmacokinetics in women with or without children with fetal alcohol syndrome. Alcohol Alcohol 39:503–508.

Kuczmarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, Wei R, Curtin LR, Roche AF, Johnson CL (2002) 2000 CDC Growth Charts for the United States: methods and development. National Center for Health Statistics. Vital Health. Stat 11(246):1–190.

Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, Amann M, Anderson HR, Andrews KG, Aryee M, Atkinson C, Bacchus LJ, Bahalim AD, Balakrishnan K, Balmes J, Barker-Collo S, Baxter A, Bell ML, Blore JD, et al. (2012) A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters

in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380:2224–2260.

Luiz DM, Barnard A, Knoesen N, Kotras N, Horrocks S, McAlinden P, Challis D, O'Connel RO (2006) Griffiths Mental Developmental Scales – Extended Revised: Two to Eight Years. Administration Manual. Hogrefe, Oxford, UK.

May PA, Blankenship J, Marais A, Gossage JP, Kalberg WO, Barnard R, de Vries M, Robinson LK, Adnams CM, Buckley D, Manning M, Jones KL, Parry C, Hoyme HE, Seedat S (2013a) Approaching the prevalence of the full spectrum of fetal alcohol spectrum disorders in a South African population-based study. Alcohol Clin Exp Res 37:818–830.

May PA, Tabachnick BG, Gossage JP, Kalberg WO, Marais A, Robinson LK, Manning MA, Blankenship J, Buckley D, Hoyme HE, Adnams CM (2013b) Maternal factors predicting cognitive and behavioural characteristics of children with fetal alcohol spectrum disorders. J Dev Behav Pediatr 34:314–325.

May PA, Brooke LE, Gossage JP, Croxford J, Adnams C, Jones KL, Robinson L, Viljoen D (2000) Epidemiology of fetal alcohol syndrome in a South African community in the Western Cape Province. Am J Public Health 90:1905–1912.

May PA, Gossage JP (2011) Maternal risk factors for fetal alcohol spectrum disorders: not as simple as it might seem. Alcohol Res Health 34:15–26.

May PA, Gossage JP, Kalberg WO, Robinson LK, Buckley D, Manning M, Hoyme HE (2009) Prevalence and epidemiological characteristics of FASD from various research methods with an emphasis on recent in-school studies. Dev Disabil Res Rev 15:176–192.

May PA, Gossage JP, Marais AS, Colleen MA, Hoyme HE, Jones KL, Robinson LK, Khaole NCO, Snell C, Kalberg WO, Hendricks L, Brooke L, Stellavato C, Viljoen DL (2007) The epidemiology of fetal alcohol syndrome and partial FAS in a South African community. Drug Alcohol Depend 88:259–271.

May PA, Gossage JP, White-Country M, Goodhart K, Decoteau S, Trujillo PM, Kalberg WO, Viljoen DL, Hoyme HE (2004) Alcohol consumption and other maternal risk factors for fetal alcohol syndrome among three distinct samples of women before, during, and after pregnancy: the risk is relative. Am J Med Genet C Semin Med Genet 127C:10–20.

Morojele NK, London L, Olorunju SA, Matjila MJ, Davids AS, Rendall-Mkosi KM (2010) Predictors of risk of alcohol-exposed pregnancies among women in an urban and a rural area of South Africa. Soc Sci Med 70:534–542.

Mphi M (1994) Female alcoholism problems in Lesotho. Addiction 89:945–949.

Nellhaus G (1968) Head circumference from birth to eighteen years. Practical composite international and interracial graphs. Pediatrics 41:106–114.

Olivier L, Urban M, Chersich MF, Temmerman M, Viljoen D (2013) Burden of fetal alcohol syndrome in a rural West Coast area of South Africa. S Afr Med J 103:402–405.

Paintner A, Williams AD, Burd L (2012) Fetal alcohol spectrum disorders — implications for child neurology, part 2: diagnosis and management. J Child Neurol 27:355–362.

Paley B (2009) Introduction: fetal alcohol spectrum disorder —shedding light on an unseen disability. Dev Disabil Res Rev 15:167–169.

Parry CD, Plüddemann A, Steyn K, Bradshaw D, Norman R, Laubscher R (2005) Alcohol use in South Africa: findings from the first demographic and health survey (1998). J Stud Alcohol 66:91–97.

Preston P (2006) Testing Children — A Practitioner's Guide to the Assessment of Mental Development in Infants and Young Children. Hogrefe, Oxford, UK.

Sharp C, Dellis A, Hofmeyer A, Kincaid H, Ross D (2014) First evidence of comorbidity of problem gambling and other psychiatric problems in a representative urban sample of South Africa. J Gambl Stud doi: 10.1007/s10899-014-9469-y [E-pub ahead of print].

Siegfried N, Parry CDH, Morojele NK, Wason D (2001) Profile of drinking behaviour and comparison of self-report with the CAGE questionnaire and carbohydrate deficient transferrin in a rural Lesotho community. Alcohol Alcohol 36:243–248.

Sobell LC, Agrawal S, Annis H, Ayala-Velasquez H, Echeverria L, Leo GI, Rybakowski JK, Sandahl C, Saunders B, Thomas S, Zioikowski M (2001) Cross-cultural evaluation of two drinking assessment instruments: alcohol timeline follow-back and inventory of drinking situations. Subst Use Misuse 36:313–331.

Stata (2013) Stata [computer program]. Release 13. Stata Corporation, College Station, TX.

Statistics South Africa (2012) Census 2011 in brief. Statistics South Africa, Pretoria. Available at: https://www.statssa.gov.za/Census2011/Products/Census_2011_Census_in_brief.pdf. Accessed July 25, 2014.

Statistics South Africa (2014) Mortality and Causes of Death in South Africa, 2011: Findings from Death Notification. Statistics South Africa, Pretoria. Available at: http://beta2.statssa.gov.za/publications/P03093/P030932011.pdf. Accessed February 2, 2015.

Thomas IT, Gaitantzis YA, Frias JL (1987) Palpebral fissure length from 29 weeks gestation to 14 years. J Pediatr 111:267–268.

Urban M, Chersich MF, Fourie LA, Chetty C, Olivier L, Viljoen D (2008) Fetal alcohol syndrome among grade 1 schoolchildren in Northern Cape Province: prevalence and risk factors. S Afr Med J 98:877–882.

Viall J, James W, Gerwel J (2011) Grape: From Slavery to BEE, pp. 132–151. Tafelberg publishers, Cape Town, ISBN 978-0-624-04938-8.

Viljoen D, Craig P, Hymbaugh K, Boyle C, Blount S (2003) Fetal alcohol syndrome – South Africa 2001. Morb Mortal Wkly Rep 52:660–662.

Viljoen DL, Gossage JP, Brooke L, Adnams CM, Jones KL, Robinson LK, Hoyme HE, Snell C, Khaole NCO, Kodituwakku P, Asante KO, Findlay R, Quinton B, Marais AS, Kalberg WO, May PA (2005) Fetal alcohol syndrome epidemiology in a South African community: a second study of a very high prevalence area. J Stud Alcohol 66:593–604.

Warren KR, Li TK (2005) Genetic polymorphisms: impact on the risk of fetal alcohol spectrum disorders. Birth Defects Res A Clin Mol Teratol 73:195–203.

World Health Organization (2014) Global status report on alcohol and health – 2014 edition. Available at: http://www.who.int/substance_abuse/publications/global_alcohol_report/en/. Accessed September 18, 2014.

4.1.3 STUDY 3

Olivier L*, **Urban M***, Chersich MF, Temmerman M, Viljoen D. Burden of fetal alcohol spectrum disorders in the rural West Coast of South Africa. *South African Medical Journal 2013; 103(6): 402-405.DOI:10.7196/SAMJ.6249.* (*Equal first author)

Burden of fetal alcohol syndrome in a rural West Coast area of South Africa

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Background. Fetal alcohol syndrome (FAS) is common in parts of South Africa; rural residence is a frequently cited risk factor. We conducted a FAS school prevalence survey of an isolated rural community in a West Coast village of Western Cape Province, so obtaining the first directly measured rate, focusing specifically on a South African rural area, of FAS and partial FAS (PFAS).
Methods. The study area (Aurora village), a community of about 2 500 people in a grain-producing region, has one primary school. All learners were eligible for study inclusion. Initial anthropometry screening was followed by a diagnostic stage entailing examination by a dysmorphologist for features of FAS, neurodevelopmental assessment, and an interview assessing maternal alcohol consumption.
Results. Of 160 learners screened, 78 (49%) were screen-positive, of whom 63 (81%) were clinically assessed for FAS. The overall FAS/PFAS rate among the screened learners was 17.5% (95% confidence interval 12.0 - 24.2%), with 16 (10.0%) children having FAS and 12 (7.5%) PFAS. High rates of stunting, underweight and microcephaly were noted in all learners, especially those with FAS or PFAS. Five (18%) mothers of affected children were deceased by the time of assessment.
Conclusion. We describe very high rates of FAS/PFAS in an isolated rural part of the Western Cape that is not located in a viticultural region. Our study suggests that the prevalence of FAS may be very high in isolated communities, or in particular hot-spots. It adds to the growing evidence that FAS/PFAS is a significant, and underestimated, health problem in South Africa. Expanded screening and surveillance programmes, and preventive interventions, are urgently needed.

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Fetal alcohol syndrome (FAS) and the less severe fetal consequences of maternal drinking, collectively described as fetal alcohol spectrum disorders (FASD) than FAS/partial FAS (PFAS), are endemic in impoverished communities of the Western and the Northern Cape provinces of South Africa (SA).[1-4] Over the past decade, levels of FAS/PFAS ranging between 40.5 and 119.4 per 1 000 have been documented in several parts of these provinces.[3,4] A recent study examined the prevalence of FASD (which is a broader and less well defined group) in an area of the Western Cape, and estimated the prevalence at between 135.1 and 207.5 per 1 000.[3]

Heavy alcohol intake during pregnancy, usually in a binge-drinking pattern, occurs in over 20% of women in the Western Cape.[6] Drinking during pregnancy remains a problem despite considerable media attention, efforts by the national government to limit alcohol harm,[7] and isolated initiatives to increase universal and other prevention activities in these provinces.[8] Heavy drinking has been socially entrenched and 'normalised' through a history including, but not restricted to, the dop system. For many women, the underlying social determinants of heavy alcohol consumption remain unchanged, and include poor socio-economic conditions, single-parent families, low levels of maternal education, concomitant use of tobacco and other substances, low religiosity and lack of alternative recreational opportunities.[6,9]

Most surveys have been conducted in small towns, and have consistently shown that FAS/PFAS is more common where mothers were resident in a rural area at the time of pregnancy.[1-3] To date, no studies have directly documented FAS/PFAS rates in entirely rural or remote parts of the country. In 2008, community leaders of a rural area in the West Coast region of the Western Cape invited our research team to assess levels of FAS/PFAS, as well as substance use, in pregnancy. The study therefore aimed to document the prevalence and risk factors for FAS/PFAS in this isolated rural community, and to provide information to assist the community to advocate for increased resources to counter substance use and related problems in the area.

Methods

The study site is a rural village (Aurora) of approximately 2 500 inhabitants. They work mostly as seasonal labourers at surrounding potato and grain farms. There is one school in the area (grades 0 - 7), at which the parents/guardians of all learners were invited to enrol in the study. Workshops were held with approximately 220 people to generate awareness of the study, with involvement of community and local government leaders, including social workers, police officers, health workers and educators from the school. The school principal and educators also attended a course on how to manage children with FASD in the classroom.

FAS diagnostic process

Prevalence of FAS and PFAS was determined by active case ascertainment using a validated two-tier screening method.[10] This entails an initial screening stage, followed by a comprehensive diagnostic stage (clinical evaluation, neurocognitive assessment and maternal interview). In the first stage, pupils were screened by a professional nurse who measured height, weight and head circumference (HC), using standard methods. Children ≤10th

percentile of the National Center for Health Statistics charts for height and weight, or ≤10th percentile for HC, were considered screen-positive and invited to the second stage.

The diagnostic stage entailed assessment by an experienced dysmorphologist (DV) for clinical features of FAS.[10] The clinical diagnosis of FAS/PFAS was substantiated by a battery of neurodevelopmental tests. Positive evidence of neurological abnormality required a HC ≤10th percentile, the presence of 'hard' signs on neurological examination, or significant abnormalities on neurocognitive assessment (below average in more than 4 of 10 scales) using primarily the Griffiths Mental Development Scale.[11]

Trained interviewers completed a semi-structured questionnaire with the mother/guardian of screen-positive children. Interviews were in the home language of participants and focused on drinking habits during the index pregnancy, which were elicited using a timeline follow-back method.[12]

The final diagnosis, based on criteria published by Hoyme *et al.* (2005),[10] encompassed all data from the clinical evaluation, the neurodevelopmental profile and maternal history. Final diagnostic categories were FAS and PFAS. The clinical diagnosis of FAS, and with less certainty PFAS, is considered distinctive even in the absence of a history of maternal alcohol use.

Study ethics and data management

Permission was obtained from the Department of Education (provincial and district) to evaluate learners and informed consent was given by the parents or legal guardians of each child. If consent was given but the child was not present for clinical or neurodevelopmental assessment, 2 further attempts were made to assess the child. Similarly, 3 attempts were made to secure maternal interviews.

A trained counsellor communicated the FASD diagnosis to the parents or guardians, as well as its implications and a proposed intervention tailored to each child. Children identified as having FAS/PFAS were referred to local government services, including speech and hearing therapists, occupational therapists, physiotherapists and social workers. With parental permission, school personnel were informed of each child's FASD status to facilitate educational support and further remedial assessment. Children with other medical conditions were referred to local and regional medical services, as required.

Intercooled Stata 12.1 (Stata Corporation, College Station, USA) was used for statistical analysis. For analysis of categorical variables, the chi-square test was used, while for continuous variables we used an unpaired Student's *t*-test or Mann-Whitney U-test for normally and non-normally distributed data, respectively.

Results

Consent for participation in the study was sought for all 171 learners in the school, of whom 160 consenting learners were available for anthropometric screening. Of the 160 screened learners, 78 (49%) were screen-positive on anthropometry, with 60 (38%) falling below the 10th percentile for both height and weight. Status regarding FAS/PFAS diagnosis was determined for 63 children (81% of screen-positives) (Table 1). Fifteen learners could not be clinically assessed because they were absent from school on all follow-up visits made to assess them.

The screened group, who were all of coloured ethnicity, were aged 4.8 - 16.4 years. About 9% (14/160) of learners were older than 14 years. Exactly half the pupils were male, though females predominated in grades 0 and 1 (62%, 32/52; p=0.04).

In the group of 160 screened learners, 16 FAS and 6 PFAS cases (13.8%; 95% CI 8.8 - 20.0) were ascertained based on full clinical assessment Mean dysmorphology score for the 16 confirmed FAS children was 17.1 (SD)±2.2, and 9.1±4.5 for children with PFAS. A further 6 were suspected of having PFAS, based on facial features

Table 1. Characteristics of grade 0 - 7 learners with fetal alcohol syndrome

Variable	All grade 0 - 7 learners (*N*=160)	Children without FAS/PFAS (*n*=132)	Children with FAS/PFAS (*n*=28)	*p*-value
Sex, *n*/*N* (%)				
Female	80/160 (50.0)	67/132 (50.8)	13/28 (46.4)	
Male	80/160 (50.0)	65/132 (49.2)	15/28 (53.6)	0.68
Age (years), *n*/*N* (%)				
4.8 - 8	59/160 (37.8)	47/132 (35.6)	12/28 (42.9)	
9 - 11	53/160 (33.6)	45/132 (34.1)	8/28 (28.6)	
12 - 16	48/160 (28.6)	40/132 (30.3)	8/28 (28.6)	0.75
School grade, *n*/*N* (%)				
0 - 1	52/160 (32.5)	40/132 (30.3)	12/28 (42.9)	
2 - 4	53/160 (33.1)	44/132 (33.3)	9/28 (32.1)	
5 - 7	55/160 (34.4)	48/132 (36.4)	7/28 (25.0)	0.37
Weight for age				
Median *Z*-score (IQR)	-1.2 (-2.1 to -0.5)	-1.0 (-1.7 to -0.4)	-2.4 (-2.9 to -1.9)	<0.001
Height for age				
Median *Z*-score (IQR)	-1.2 (-1.9 to -0.7)	-1.0 (-1.8 to -0.5)	-2.1 (-2.5 to -1.5)	<0.001
BMI for age				
Median *Z*-score (IQR)	-0.7 (-1.4 to -0.1)	-0.6 (-1.3 to 0.1)	-1.4 (-2.1 to -0.7)	0.001
Head circumference				
3rd - 10th percentile, *n*/*N* (%)	20/160 (12.6)	13/131 (9.9)	7/28 (25.0)	
≤3rd percentile, *n*/*N* (%)	30/160 (18.9)	13/131 (14.0)	17/28 (60.7)	<0.001

IQR = interquartile range; BMI = body mass index; FAS = fetal alcohol syndrom; PFAS = partial fetal alcohol syndrome

of FAS, HC <10th percentile, and a history of maternal alcohol use, but did not have a neurodevelopmental assessment. Despite the lack of this assessment, they had sufficient features to meet the Hoyme criteria for PFAS or FAS.[9] They were assigned as PFAS cases, and included as such for further analysis, bringing the total to 28 affected children (17.5%; 95% CI 12.0 - 24.2).

No associations were detected between having FAS/PFAS and gender or grade. Children with FAS/PFAS were a median 8.5 years old, while other children were a median 10.0 years (p=0.09). The median body mass index of children without FAS/PFAS was 15.8 kg/m^2 (IQR 14.6 - 17.5), compared with a median 14.7 kg/m^2 in children with FAS/PFAS (IQR 13.7 - 15.6; p=0.001). The entire cohort of children, and especially those with FAS/PFAS, showed very high levels of stunting and were underweight for age (Table 1).

Five (18%) of the mothers of the 28 subjects with FAS/PFAS had died, and in 2 instances the father was also known to have died. The study team referred 20 children to the school psychologist.

Discussion

Researchers have previously noted that levels of FAS/PFAS in parts of the Western and Northern Cape provinces are several times higher than elsewhere in the world.[1] Our data represent the first directly measured FAS/PFAS prevalence data from an entirely rural community in SA, and demonstrate levels that are high even when compared with similar local studies.

Table 2 shows FAS rates across published school prevalence studies in SA. Although direct comparisons between studies can be misleading, all these school surveys used similar methodologies, except that ours is the only study to include learners beyond first grade (there was, however, no significant difference in the prevalence of FAS across school grades).

Though the FAS rate of 10% in Aurora is very high, the true scale of overall FASD is certainly considerably higher. A further 7.5% of children were assessed as having FAS/PFAS, although this assessment was complicated by some participants not completing all study procedures, owing mostly to truancy from school (teachers suspected a high FASD rate among truant children). In addition to study-specific issues, it is likely that FASD prevalence studies inherently underestimate its prevalence because of the difficulties in diagnosing subjects without typical facial features, and in older children and adolescents as children age.[13] In this regard, the high rate of non-syndromic microcephaly found in 'unaffected' children may relate, in part, to sub-clinical cases of FASD.

The high prevalence of FAS/PFAS in the village of Aurora is consistent with: (*i*) the rural-urban gradient in FAS prevalence shown in Table 2, (*ii*) studies that show a higher FAS/PFAS rate in children born in rural than urban areas,[1-4] and (*iii*) evidence that binge drinking is more prevalent in rural (20%) than urban informal (16%) and urban formal (15%) areas.[15] FASD also appears more prevalent in very isolated communities – the communities with the highest published prevalence of FAS/PFAS (Aurora and De Aar) are very isolated geographically. Conversely, high rates do not appear to relate to the presence of viticulture in an area.

Despite mounting evidence from school surveys and other sources that FASD is a significant public health problem, it remains under-recognised. For example, the Western Cape Burden of Disease study considered FASD only inasmuch as it is a cause of low birthweight, rather than as a significant cause of morbidity, mortality and disability in its own right.[16] In part because it is under-recognised, there is a dearth of local measures aimed at preventing FASD, despite international acceptance of the utility of a range of interventions to reduce alcohol-related harm, ranging from policy and community level approaches to setting-specific approaches such as 'brief interventions' in prenatal care.[17] As a local example of a successful intervention, we have reported a 30% reduction in FAS/PFAS rates associated with a community-level intervention comprising intensive 'universal prevention' measures.[18]

Interventions within the health sector that should be implemented, upgraded or urgently investigated include: (*i*) strengthened family planning services; (*ii*) improved antenatal education regarding the risks of drinking; (*iii*) identification of risky drinking in pregnancy and implementation of brief interventions to reduce it; (*iv*) strategies aimed at early identification of FASD to allow early intervention in the child and prevention of recurrence in future children; and (*v*) national-level surveillance of risky drinking and FASD rates to improve data on the problem of FASD.

Table 2 indicates that, although there is a high level of FAS in many parts of SA, the prevalence varies. A systematic approach is needed for determining overall FASD levels in the country that is both wide in scope but also provides local actionable detail in higher-risk areas. We recommend regular surveillance of a systematic sample of schools and/or antenatal clinics across the country, which would allow provincial and national baseline rates to be established and monitored over time, and would inform more intensive and cost-effective targeting of communities at highest risk.

We found that nearly 1 in 5 of mothers to children with FAS/PFAS were deceased. This phenomenon has not been studied in detail to date, although it is noteworthy that the 3 Wellington studies[1-3] reported significant maternal mortality in mothers of FAS/PFAS children. Collectively, they report 13 (7%) maternal deaths among 185 mothers of children with FASD by the time the index cases were assessed at about 7 years of age. Causes of death, where known, appeared to be potentially associated with alcohol use, including accidents such as house fires; homicide and

Table 2. FAS prevalence rates from studies among schoolchildren in diverse South African communities

Site	Site description	Viticultural area (Y/N)	FAS cases*/sample size† (cases per 1 000)
Gauteng[13]	Metropole	N	16/830 (19.3)
Wellington, Western Cape[1]	Town	Y	46/992 (46.5)
Wellington, Western Cape[2]	Town	Y	64/863 (74.2)
Wellington, Western Cape[3]	Town	Y	55/818 (67.2)
Upington, Northern Cape[4]	Town	Y	69/1 299 (53.1)
De Aar, Northern Cape[4]	Isolated town	N	54/536 (100.7)
Aurora, Western Cape	Isolated village	N	16/160 (100.0)

†To maximise comparability, data are restricted to fully assessed FAS cases divided by the number actually screened.
*Excludes PFAS cases.

other violent death; pulmonary tuberculosis; and liver disorders. These data are consistent with evidence that binge drinking, in addition to being associated with FASD, is also strongly associated with unintentional injury, interpersonal violence, unsafe sex and other negative health consequences for adults.[19,20] A case of FASD should therefore be considered as a marker for adverse maternal health consequences.

This study aims to benefit the local population, NGOs and community-based organisations, as well as inform government departments, specifically Health, Education, Social Services and Agriculture. The study heightened the community's awareness of substance abuse problems and FASD in particular. Although this district has not featured on the government's priority list for high-risk substance abuse areas and/or other health needs to date, the community specifically requested that the study findings be publicised and used to rectify this omission. Findings will also inform development of a comprehensive NGO-led intervention to address these local problems.

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Conflict of interest statement. The FARR receives funding from the Industry Association for Responsible Alcohol Use (ARA) and donations from the Whiskey Live Festival.

Authorship. L Olivier and M Urban are equal first authors.

References

1. May PA, Brooke LE, Gossage JP, et al. Epidemiology of fetal alcohol syndrome in a South African community in the Western Cape Province. Am J Public Health 2000;90(12):1905-1912. [http://dx.doi.org/10.2105%2FAJPH.90.12.1905]
2. Viljoen DL, Gossage JP, Brooke L, et al. Fetal alcohol syndrome epidemiology in a South African community: a second study of a very high prevalence area. J Stud Alcohol 2005;66(5):593-604.
3. May PA, Gossage JP, Marais AS, et al. The epidemiology of fetal alcohol syndrome and partial FAS in a South African community. Drug Alcohol Depend 2007;88(2-3):259-271. [http://dx.doi.org/10.1016%2Fj.drugalcdep.2006.11.007]
4. Urban M, Chersich MF, Fourie LA, et al. Fetal alcohol syndrome among grade 1 schoolchildren in Northern Cape Province: prevalence and risk factors. S Afr Med J 2008;98(11):877-882.
5. May PA, Blankenship J, Marais A-S, et al. Approaching the prevalence of the full spectrum of fetal alcohol spectrum disorders in a South African population-based study. Alcohol Clin Exp Res 2012 Dec 14. (Epub ahead of print) [http://dx.doi.org/ 10.1111/acer.12033] (accessed 19 March 2013).
6. Croxford J, Viljoen D. Alcohol consumption by pregnant women in the Western Cape. S Afr Med J 1999;89(9):962-965.
7. South African Revenue Services. Excise duties and levies 2012. http://www.sars.gov.za/home.asp?pid=483 (accessed 1 May 2012).
8. Chersich MF, Urban M, Olivier L, et al. Universal prevention is associated with lower prevalence of fetal alcohol spectrum disorders in Northern Cape, South Africa: a multicentre before-after study. Alcohol Alcohol 2012; 7(1):67-74. [http://dx.doi.org/10.1093%2Falcalc%2Fagr145]
9. Viljoen D, Croxford J, Gossage JP, et al. Characteristics of mothers of children with fetal alcohol syndrome in the Western Cape Province of South Africa: a case control study. J Stud Alcohol 2002;63(1):6-17.
10. Hoyme HE, May PA, Kalberg WO, et al. A practical clinical approach to diagnosis of fetal alcohol spectrum disorders: clarification of the 1996 Institute of Medicine Criteria. Pediatrics 2005;115:39-47. [http://dx.doi.org/10.1542%2Fpeds.2005-0702]
11. Griffiths R. The Ability of Young Children: A Comprehensive System of Mental Measurement for the First Eight Years of Life. Oxford, UK: The Test Agency, 1970.
12. Sobell LC, Agrawal S, Annis H, et al. Cross-cultural evaluation of two drinking assessment instruments: alcohol timeline followback and inventory of drinking situations. Subst Use Misuse 2001;36(3):313-331. [http://dx.doi.org/10.1081%2FJA-100102628]
13. Alberta Partnership on Fetal Alcohol Syndrome. Diagnosis of fetal alcohol syndrome. Can Child Adol Psych Rev 2003;12(3):81-86.
14. Viljoen D, Craig P, Hymbaugh K, et al. Fetal alcohol syndrome - South Africa 2001. MMWR 2003;52(28):660-662.
15. Harker N, Kader R, Myers B, et al. Substance abuse trends in the Western Cape, a review of studies conducted since 2000. http://www.sahealthinfo.org/admodule/substance.pdf (accessed 22 April 2012).
16. Sanders D, Reynolds L, Eley B, et al. Western Cape Burden of Disease Reduction Project Volume 7: Decreasing the Burden of Childhood Disease, 2007. http://www.westerncape.gov.za/eng/pubs/reports_research/W/157844 (accessed 20 May 2012).
17. Monteiro M. The road to a World Health Organization global strategy for reducing the harmful use of alcohol. Alc Res Health 2011;34(2):257-260.
18. Chang G. Screening and brief intervention in prenatal settings. Alcohol Res Health 2005;55:80-84.
19. Naimi TS, Brewer RD, Mokdad A, et al. Binge drinking among US adults. JAMA 2003;289(1):70-75. [http://dx.doi.org/10.1001%2Fjama.289.1.70]
20. Razvodovsky YE. Contribution of alcohol in accident related mortality in Belarus: a time series approach. J Inj Violence Res 2012;4(2):58-64.

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4.2 COMPARISON OF MOTHERS TO CHILDREN WITH FAS IN THREE DIVERSE SETTINGS

4.2.1 STUDY 4

Urban MF, Olivier L, Louw JG, Lombard C, Viljoen DL, Scorgie F, Chersich MF. Changes in drinking patterns during and after pregnancy among mothers of children with fetal alcohol syndrome: A study in three districts of South Africa. Drug Alcohol Depend. 2016 Nov 1;168:13-21. doi: 10.1016/j.drugalcdep.2016.08.629.

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Full length article

Changes in drinking patterns during and after pregnancy among mothers of children with fetal alcohol syndrome: A study in three districts of South Africa

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ABSTRACT

Background: Mixed ancestry populations in South Africa have amongst the highest rates of fetal alcohol syndrome (FAS) worldwide. Defining the drinking patterns of women with a FAS child guides FAS preventive interventions.
Methods: Data were drawn from FAS prevalence surveys conducted in three districts: Witzenberg (Cape Winelands), Frances Baard (inland mining town) and Saldanha Bay (coastal towns). 156 mothers and 50 proxy informants of school-entry children diagnosed with FAS and partial-FAS were interviewed, and compared with 55 controls recruited in Saldanha Bay.
Results: Study participants were of low socio-economic status (SES), and a majority of children were either in foster care (12%) or had been cared for by relatives for long periods (44%). Of cases, 123/160 (77%) reported current drinking, similar between sites. During pregnancy, only 35% (49/139) of cases had stopped drinking, varying between sites (from 21% to 54% in chronological order of surveys; $p < 0.001$), while 6% (7/109) increased drinking. Though many women who stopped in pregnancy resumed postpartum, cessation in pregnancy was strongly associated with discontinuation in the long run (OR = 3.3; 95%CI = 1.2–8.9; $p = 0.005$). At interview, 36% of cases (54/151) and 18% of controls (9/51) were at risk of an alcohol-exposed pregnancy ($p = 0.02$). Median maternal mass of cases was 22 kg lower than controls, with 20% being underweight and 14% microcephalic.
Conclusions: Increasing rates of drinking cessation during pregnancy over time suggest rising awareness of FAS. Cessation is associated with recidivism after pregnancy but also with reduced long-term drinking. Interventions should target alcohol abstinence in pregnancy, but extend into the puerperium.

1. Introduction

Alcohol use in pregnancy is associated with a risk of fetal alcohol syndrome (FAS), partial FAS (PFAS, and jointly abbreviated as P/FAS), and other diagnoses within the cluster of fetal alcohol spectrum disorders (FASD). Regular binge-drinking is the major risk factor, but risk is modified by many other factors (Abel and Hannigan, 1995). May and Gossage (2011) cluster these factors into three categories. Exposures include binge-drinking, smok-

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0376-8716/

ing and drug use, and poor nutrition. Host factors include more advanced age, high gravidity and parity, short stature and low body mass index (BMI), depression and genetics. Environmental factors include low socioeconomic status (SES), social isolation, family and cultural factors, and limited awareness of FASD.

Some regions of South Africa have high rates of P/FAS, with published figures ranging from 2.7% (Viljoen et al., 2003) to 11.9% (Urban et al., 2008). The prevalence of P/FAS is well documented in the Cape Winelands district of the Western Cape Province (May et al., 2000, 2007, 2013a; Viljoen et al., 2005), but information is limited in other settings (Viljoen et al., 2003; Urban et al., 2008, 2015).

About 14% of South African women binge-drink, with rates varying by ethnic group, urban and rural areas and province, with high rates in the Western Cape and Northern Cape. Levels of binge drinking in women of mixed racial ancestry, designated South African 'Coloured' (SAC) by the census, are as high as in their male counterparts, and considerably higher than women in other ethnic groups (Department of Health and Medical Research Council, 2007).

For this reason, most participants in previous South African prevalence surveys have come from the SAC population group, a highly admixed population whose roots – indigenous Khoisan, European, Black African, and South and South-East Asian – reflect the unique history of the Cape Colony and South Africa.

Comprising only 9% of the South African population (Statistics South Africa, 2012), the SAC group experienced a long history of oppression under colonial and then Apartheid rule. In the colonial era, a regular allowance of wine was given to slaves on the wine farms, and after emancipation in the 1830s, this evolved into the 'Dop' system, whereby weekly wages were supplemented with cheap alcohol. This remained prevalent on farms in the Western Cape Province until as late as the 1990s (London, 1999). The 'Dop' system is popularly credited with entrenching risky drinking practices, at least on wine farms in the Western Cape Province.

A detailed understanding of the at-risk populations and their drinking patterns is important for developing appropriate FAS prevention strategies. To date, interventions to reduce alcohol harm in South Africa have focused largely on broad policy measures, e.g., increased taxation and awareness-raising. These have had mixed results, with binge drinking even increasing over time, and particularly so among females (Ramsoomar and Morojele, 2012). Additional measures such as 'screening, brief intervention and referral to treatment' have been proven effective in reproductive age women both internationally (Floyd et al., 2009) and in South Africa (Rendall-Mkosi et al., 2013). Such selective interventions require more detailed insight into target populations, and to date have not been implemented beyond a handful of sites. With this in mind, we compared mothers of children with P/FAS (cases) and control mothers, to identify factors relevant to designing preventive interventions in the SAC population.

2. Methods

2.1. Survey sites and study population

Since the 1990s, about 10 FAS prevalence surveys have been performed – at the request of government departments – by the Foundation for Alcohol Related Research (FARR; http://www.farrsa.org.za), a not-for-profit organization that brings together a range of health professionals.

Surveys were included in this study if they used a similar approach to FAS diagnosis (described by Hoyme et al., 2005), and enrolled a representative group of school-entry children. Three surveys met these criteria. These surveys entailed successive screening and diagnostic phases to detect cases of P/FAS. The diagnostic procedures are described in detail elsewhere (Urban et al., 2015). Maternal interviews were conducted if clinical features indicated a high risk of FAS.

The first survey, in 2008, was carried out in Witzenberg (WB) sub-district of the Cape Winelands district, Western Cape Province. 18 primary schools were included, which were in the town of Ceres (population 30,000), in several smaller towns, or on farms. Prevalence of combined P/FAS was 8.7% (88 cases in 1010 enrolled children) and of FAS was 5.0% (51/1010; unpublished data). WB is a viticulture and fruit farming region where the 'Dop' system was widespread until the early 1990s (London, 2003).

The second survey was conducted in 2012, in Frances Baard (FB) district municipality, Northern Cape Province. It found a 5.7% (89 of 1587 enrolled) prevalence of P/FAS, and 5.2% (83/1587) of FAS (Urban et al., 2015). FB is a long-established, now economically depressed, mining town (population 236,000). It is located in a semi-arid region, approximately 1000 km inland from the other sites.

The third survey was held in 2013 in the largely urban Saldanha Bay (SB) sub-district of the West Coast district, Western Cape Province. Here the prevalence of P/FAS was 6.4% (99 cases in 1540 enrolled children) and FAS 4.7% (73/1540; unpublished data). This site is approximately 180 km north-west of WB. It includes the town of Vredenburg (population 38,000), the harbour town of SB (population 28,000), and surrounding coastal villages. Economic activity relates predominantly to shipping and fishing.

Interviews with mothers (or proxies) of children with P/FAS were included in this analysis if the mother was of SAC ethnicity, as indicated by the mother herself or a proxy informant. Interviews at one site with mothers (or proxies) of a randomly selected group of children without P/FAS were included as controls using the same ethnicity criteria. People of SAC ancestry comprise a majority of the population in the SB and WB sites, but a minority in the inland FB site.

2.2. Interviews

Professional study staff or community workers were trained to carry out interviews, which were conducted with the mother of the index case, or with a proxy informant (usually close family member) if the mother was unavailable after two tracing attempts. Information was less complete from proxies than mothers, causing variation in the denominator between study variables.

Interviewers used a semi-structured questionnaire to elicit information on the mother's history of alcohol and substance use, drinking context, self-perception of her drinking, demographics, SES and reproductive health. Anthropometric measurements of the mother were also performed.

The questionnaire was adapted from a previous validated tool (Viljoen et al., 2002). While the questions and general flow of the questionnaire were mostly identical across sites, the length was reduced from 114 items in the earliest survey, to 101 items thereafter. This was achieved by decreasing the number of free-text probes, or the number of questions addressing a specific topic. In some instances, additional questions were added. Where the data permitted, questions were recoded to create a variable common to all sites.

History of alcohol consumption in pregnancy was elicited by asking for recent drinking practices, then drinking practices prior to the index pregnancy, and any changes during and shortly after the pregnancy. Similar questionnaires for retrospective report of alcohol use have been validated in several populations (Sobell et al., 2001). Reported alcohol use was expressed as the number of standard drinks consumed, with a standard drink being defined

as one containing 14 g of absolute alcohol (National Institute on Alcoholism and Alcohol Abuse, 2005). Reported use of four or more standard drinks on a day was designated as an episode of binge drinking. Women who were pregnant or not using contraception were described as at risk for alcohol-exposed pregnancy (AEP) if they were drinking, or at high risk for AEP if binge drinking in the last three months – as suggested by Balachova et al. (2015).

Women's anthropometric measurements were obtained using standard methods and compared to charts for height, weight and body mass index (BMI) of the Centers for Disease Control (2005), and for head circumference of Nellhaus (1968). Underweight was defined as a BMI of <18.5 kg/m^2 and obesity as a BMI of ≥30 kg/m^2.

Internal control questions were included to test validity of responses, and responses were generally consistent. Interviewers qualitatively assessed each interview for reliability of information received.

2.3. Statistical analysis

Intercooled Stata 13 (StataCorp, Texas) was used to merge and recode questionnaire databases, and conduct statistical analysis. Univariate analysis compared controls to all cases, the main focus of the paper (Tables 1 and 2). Cases in the three sites were also compared, described as 'inter-site variation', and these findings are mentioned where they illustrate key points relevant to a future intervention. Categorical data were analysed using the Pearson chi square, or Fisher exact tests. Ordinal and continuous data were analysed with the Student's *t*, Kruskal-Wallis, or one-way Anova tests, as applicable.

2.4. Ethics

IRB approval was granted by the Health Research Ethics Committee of the University of Stellenbosch (N13/01/008). The study was approved by the Department of Social Development at provincial level. Consent was individually obtained from the mother or guardian of each child. Confidentiality was maintained by appropriate training of staff, storing records in a locked room, and ensuring that electronic records were password protected.

3. Results

3.1. Participants (Fig. 1)

Of 346 women with a P/FAS child, 261 (75%) were included in the analysis: 206 (79%) cases, and 55 (21%) controls. Two thirds of case women had a child with FAS (141, 68%), and a third with PFAS (65, 32%). 156 (76%) case interviews were with mothers and 50 (24%) with proxy informants. Mean time elapsed between index pregnancy and interview was 7.6 (SD = 0.72) years for controls and 8.0 (2.3) years for cases (p = 0.27).

3.2. Alcohol and other substance use (Table 1)

3.2.1. Drinking history. A history of ever drinking was several fold higher in cases than controls (OR = 8.1; 95%CI = 2.1–37.5; p < 0.001). A higher proportion of all cases than controls initiated drinking before 16 years of age (15% versus 2%; p = 0.03). Eight (5%) of 175 cases had received 'Dop' in the past, of whom 7 were from WB (p = 0.02).

3.2.2. Drinking in pregnancy. Of 206 case interviews, 36 (17%) did not provide information about drinking in pregnancy – mostly because proxy informants lacked knowledge of the mother's drinking status (33 cases). Twenty women denied drinking in pregnancy, of whom 10 were considered reliable informants (5% of P/FAS cases).

Fig. 2 compares the proportion of women who were drinking at several time intervals, from shortly before pregnancy until the time of interview. Among cases, cessation of drinking in pregnancy varied by site from 21% (13 of 62) in WB, and 26% (5 of 19) in FB, to 54% (32 of 59) in SB (p < 0.001). Most resumed drinking within 12 months but, despite this, case women who had stopped drinking in pregnancy were 3.3 fold more likely to currently abstain from drinking than those who drank throughout pregnancy (OR = 3.3; 95%CI = 1.2–8.9; p = 0.005).

Fig. 3 gives additional detail about changes in actual amounts drank during pregnancy, compared to pre-pregnancy levels for each site. This was based on information from 121 cases or control drinkers who gave information that was sufficiently detailed and considered reliable by the interviewers. 8 (7%) women, including one control, started or increased drinking in pregnancy – more often in WB than elsewhere (p = 0.04). Among 109 cases, 62 (57%) either stopped or reduced drinking in pregnancy.

3.2.3. Current drinking. Three quarters of cases reported drinking in the past year, much higher than controls (OR = 5.3; 95%CI = 2.6–10.0; p < 0.001). Most cases were current binge drinkers, with inter-site variation in prevalence of least one episode per month (WB 38/50 [76%], FB 16/20 [80%], SB 28/51 [55%]; p = 0.04). Virtually all were primarily weekend drinkers, with 67 (50%), 112 (83%) and 39 (29%) of 135 cases drinking on Fridays, Saturdays and Sundays respectively.

3.2.4. Drinking companions and location. Most cases and controls drank with friends or family, and at someone's home, with few drinking alone or in public spaces. Frequency of drinking with partners was similar across cases at the different sites, but WB cases more often had a heavy-drinking partner in pregnancy than other sites (37/50 [74%], p < 0.001).

3.2.5. Mother's perception of her drinking. A majority of drinkers at all sites had previously tried to reduce drinking. Self-perception of having a drinking problem, however, was low and varied between sites (WB 15/55 [27%], FB 3/20 [15%], SB 2/70 [4%]; p < 0.001). These figures closely paralleled their perception of need for treatment.

3.2.6. Other substance use. Smoking was much more common among cases than controls, and especially among WB cases (WB 51/51 [100%]; p < 0.001). Other drugs were reported by a small minority.

3.3. Demographic, socio-economic, reproductive health and anthropometric characteristics (Table 2)

3.3.1. Demographics and socio-economics. As with the SAC population more generally, more than 95% of women were Afrikaans speaking. There were some inter-site differences between cases, most strikingly between WB and the two urban sites (FB and SB).

Fewer cases than controls were married, with the majority cohabiting in WB (33/63 [52%]), but being single parents at the two urban sites (51/92 [55%]). In WB, educational level was lower, with almost half not having completed primary education (29/62 [47%]), but there were also lower rates of unemployment (12/66 [18%]) and of informal housing in this site (4/68 [6%]). The inland FB site had particularly high rates of unemployment (18/22 [82%]) and of informal housing (8/22 [36%]). Income was low among both cases

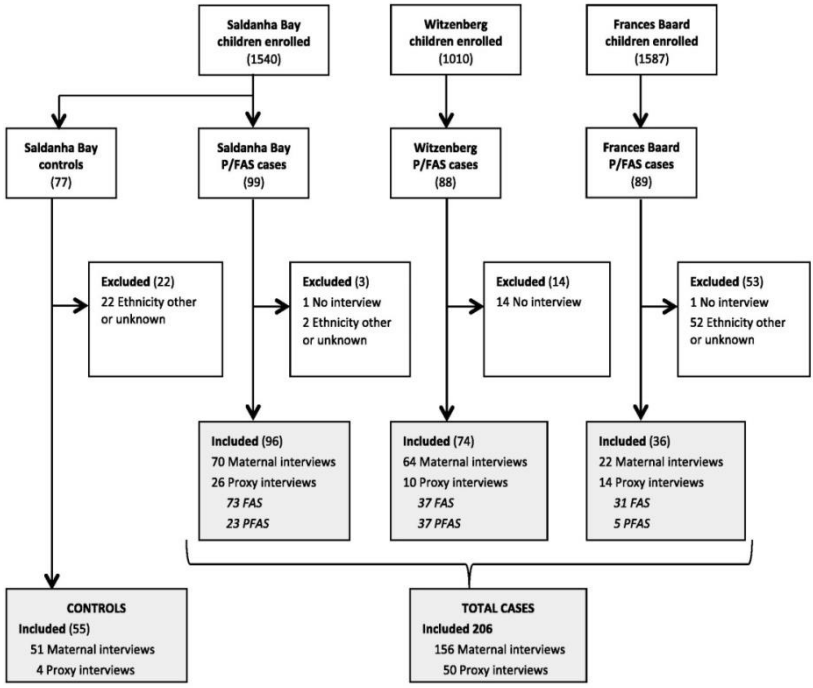

Fig. 1. Flowchart of participant selection.

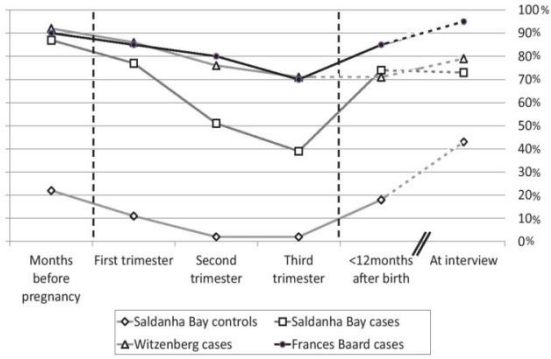

Fig. 2. Percentage of women drinking per site, before, during and after pregnancy.

Table 1
Alcohol and substance use among control women, and all cases at three sites in South Africa.

Variable	SB controls (N = 55)	Total cases (N = 206)	*P*
Drinking Onset and 'Dop'			
Ever drank alcohol n/N (%)	42/51 (82%)	152/156 (97%)	<0.001
Mean age initiated drinking (SD) N	19.4 (3.4) 42	18.7 (3.4) 139	0.22
Mean age started drinking regular ly(SD) N	22.7 (4.6) 39	21.8 (4.7) 130	0.26
Ever received 'Dop' n/N (%)	0/55 (0%)	8/175 (5%)	0.20
Drinking in pregnancy			
Any alcohol in pregnancy n/N (%)	12/51 (24%)	150/170 (88%)	<0.001
Stopped drinking in pregnancy	11/12 (92%)	49/139 (35%)	<0.001
Changes in drinking in pregnancy[a]			
Still drinking at end of 1st trimester n/N (%)	5/12 (42%)	101/109 (93%)	<0.001
Still drinking at end of 2nd trimester n/N (%)	1/12 (8%)	84/109 (77%)	<0.001
Still drinking at end of 3rd trimester n/N (%)	1/12 (8)	73/109 (67%)	<0.001
Reduced drinking by 3rd trimester n/N (%)	1/12 (8%)	26/109 (24%)	0.30
Unchanged drinking by 3rd trimester n/N (%)	0/12 (0%)	41/109 (38%)	0.008
Increased at any time in pregnancy n/N (%)	1/12 (8%)	7/109 (6%)	0.58
Current alcohol use			
Alcohol use in past year n/N (%)	22/51 (43%)	123/160 (77%)	<0.001
Drinks on ≥1 weekend/month n/N (%)[b]	7/22 (32%)	82/121 (68%)	0.001
≥4 drinks per occasion n/N (%)[b]	15/20 (75%)	82/117 (70%)	0.66
Median alcohol units/weekend (IQR) N[b]	6 (3–6) 20	8.3 (5–13.5) 120	0.05
Risk of AEP: n/N (%)			
At risk	9/51 (18%)	54/151 (36%)	0.02
At high risk	4/51 (8%)	41/151 (27%)	<0.001
Alcohol type			
Beer	11/22 (50%)	88/135 (65%)	0.17
Cider or alcopop	8/22 (36%)	13/135 (10%)	0.001
Wine	5/22 (23%)	30/135 (22%)	0.96
Spirits	3/22 (14%)	13/135 (10%)	0.56
Homebrew	0/22 (0%)	0/135 (0%)	–
Drinking companions: n/N (%)			
Drinks alone	1/20 (5%)	12/105 (11%)	0.69
Partner[c]	6/36 (17%)	26/83 (31%)	0.47
Family	7/20 (35%)	32/105 (30%)	0.69
Friends	12/20 (60%)	57/105 (54%)	0.64
Partner drank heavily in index pregnancy[c]	8/31 (26%)	50/90 (56%)	0.004
Drinking location: n/N (%)			
At a home	18/18 (100%)	101/104 (97%)	1.0
In tavern	0/20 (0%)	3/104 (3%)	1.0
Outdoors	1/18 (6%)	5/106 (5%)	1.0
Mother's perception of her drinking: n/N (%)			
Drinking ever a problem	1/51 (2%)	20/145 (14%)	0.02
Drinking currently a problem	0/51 (0%)	9/141 (6%)	0.12
Has tried to stop or reduce drinking	28/37 (76%)	111/136 (82%)	0.42
Ever treated for drinking problem	0/51 (0%)	1/136 (1%)	1.0
Wants alcohol treatment	0/51 (0%)	18/132 (14%)	0.004
Other substance use: n/N (%)			
Smoked in pregnancy	23/51 (45%)	118/141 (84%)	<0.001
Ever used drugs other than alcohol	1/50 (2%)	8/140 (6%)	0.44

SD standard deviation; IQR Interquartile range.
[a] Excludes possible unreliable histories.
[b] Of drinkers.
[c] If married or cohabiting.

and controls, although lower in cases (note that the comparison is affected by the time gap between studies).

3.3.2. Other social. In keeping with the predominantly social pattern of drinking, case women were unlikely to be socially isolated, though they were less likely than controls to have a best friend. A majority of case children had either spent an extended period in the care of other relatives or were in foster care. Foster care was much more common in cases than controls (OR = 7.5, 95%CI = 1.3–42; p = 0.02), and was often due to maternal death.

3.3.3. Reproductive health. Most index pregnancies were unplanned. Pregnancy confirmation and first antenatal visit occurred after the first trimester in 40% and 48% of women respectively. At interview, 9 (4%) of 201 women were pregnant, of whom 5 were drinking. Current use of contraception was similar among drinkers (72/130 [55%]) and non-drinkers (35/62 [56%], p = 0.89). Risk of AEP, and high risk of AEP (see Table 1), were over twice and three times higher in cases than controls respectively.

3.3.4. Anthropometry. Control women were of relatively short stature, but average BMI was in the obese range. Cases were of much lower mass and BMI than controls. Cases in FB had a particularly low median mass (47 kg [IQR 41-60]) and a high prevalence of underweight BMI (9/21 [43%]). Fourteen percent of case women had a head circumference below the 3rd centile (20/142).

Table 2
Demographic, socio-economic, reproductive and anthropometric characteristics of control women, and women with an affected child, at three sites in South Africa.

Variables	SB controls (N = 55)	Total cases (N = 206)	P
Demographics			
Median age at birth of index child (IQR) N	29.3 (22.5–34.4) 53	29.0 (23.0–33.0) 181	0.73
Years of education completed: n/N (%)			
0–6 years	8/54 (14%)	53/179 (30%)	0.006
7–11 years	33/54 (61%)	109/179 (61%)	
≥12 years	13/54 (24.1%)	17/179 (10%)	
Member of religious group n/N (%)	54/54 (100%)	165/180 (92%)	0.03
Marital status in index pregnancy: n/N (%)			
Married	18/51 (35%)	24/155 (15%)	
Single	19/51 (37%)	66/155 (43%)	
Cohabiting	14/51 (27%)	63/155 (41%)	
Other	0/51 (0%)	2/155 (1%)	0.02
Socioeconomic status			
Employment: n/N (%)			
Fulltime	19/54 (35%)	50/165 (30%)	
Part time	8/54 (15%)	24/165 (15%)	
Seasonal	7/54 (13%)	18/165 (11%)	
Unemployed, seeking work	20/54 (37%)	68/165 (41%)	
Unemployed, not seeking work	0/54 (0%)	5/165 (3%)	0.78
Median monthly household income in ZAR (IQR) N	3300 (1950–7100) 51	2390 (1180–4200) 125	0.004
Housing type: n/N (%)			
House	45/51 (88%)	135/159 (85%)	
Informal structure	6/51 (12%)	24/159 (15%)	0.55
Other social			
Friendships			
Has a best friend	41/51 (80%)	90/153 (59%)	0.005
Has no friends at all	0/51 (0%)	7/153 (5%)	0.12
Household size:			
Median adults in home (IQR) N	2 (1–3) 155	2 (1–3) 46	0.87
Median children in home (IQR) N	2 (2–3) 150	3 (2–4) 49	0.71
Median years living in home (IQR)	15 (7–15) 51	15 (5–25) 151	0.93
Childcare: n/N (%)			
Child in formal foster care	1/55 (2%)	25/206 (12%)	0.01
Child cared for by relatives for extended periods	13/54 (24%)	80/181 (44%)	0.02
Mother deceased n/N (%)	1/55 (2%)	15/206 (7%)	0.21
Reproductive health			
Mean times pregnant (SD) N	3.7 (1.7) 51	3.5 (1.6) 158	0.33
Mean live births (SD) N	3.4 (1.8) 51	2.9 (1.6) 150	0.08
Index pregnancy unplanned n/N (%)	33/51 (65%)	118/156 (76%)	0.13
Median gestation at pregnancy confirmation [months] (IQR) N	3 (1–4) 50	3 (3–5) 146	0.07
Median gestation at 1 st antenatal visit [months] (IQR) N	4 (2–5) 50	3 (3–5) 146	0.56
Current use of contraception n/N (%)	29/49 (59%)	78/146 (53%)	0.48
Anthropometry			
Median height (IQR) [cm] N	157.5 (152–162) 48	155 (150–158) 148	0.03
Height <3rd centile n/N (%)	10/48 (21%)	40/147 (27%)	0.38
Median mass (IQR) [kg] N	76 (58–83) 51	54 (45–70) 148	<0.001
Mass <3rd centile n/N (%)	3/51 (6%)	34/148 (23%)	0.006
Median BMI (IQR) [kg/m^2] N	30.0 (23.7–32.7) 48	23.0 (19.6–28.8) 147	<0.001
BMI <18.5 kg/m^2	4/48 (8%)	29/146 (20%)	0.08
Median head circumference (IQR) [cm] N	55 (53.8–57) 46	54 (53–55.5) 142	0.002
Head circumference <3rd centile n/N (%)	3/46 (7%)	20/142 (14%)	0.17

SD standard deviation; IQR Interquartile range; ZAR = South African Rands.

4. Discussion

This study compares mothers of over 200 children with P/FAS with control women, and extends knowledge of P/FAS prevalence, maternal drinking practices and other risk factors for P/FAS in a highly vulnerable population. Controls displayed similar drinking rates (ever, current and binge episodes) to those in a recent population-based study among rural women of the same district (SB) (Morojele et al., 2010), suggesting that their drinking rates are representative of the area's general population. The prevalence of P/FAS was above 5% in all three sites, although highest at the WB site, which was expected, as it is a more rural site and situated in the Cape Winelands – both factors considered major risks for FAS.

Two aspects of women's drinking that are especially pertinent to P/FAS risk are frequency of binge drinking and whether the woman stops drinking in pregnancy. Our study sheds light on cessation versus continuation of drinking during pregnancy, as well as changes in the volume drank during pregnancy. Over 90% of control women reported cessation in pregnancy, compared to only a third to a half of P/FAS women. Rates of cessation of drinking among con-

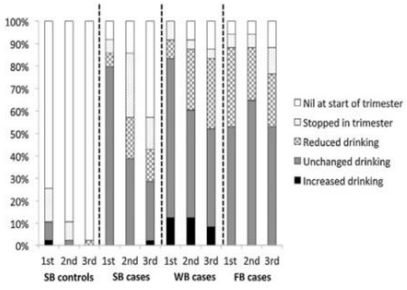

Fig. 3. Women's drinking patterns in each pregnancy trimester, compared to pre-pregnancy, by site.

trol women are comparable to reductions of binge drinking found among pregnant women in other populations outside South Africa (Fortin et al., 2015; Balachova et al., 2011). Stopping or reducing drinking is clearly important, but the presence of P/FAS in case children whose mothers had stopped, demonstrates that it is often 'too little, too late', in part because recognition of pregnancy was often delayed.

Sites with higher rates of cessation showed greater increases in drinking *after* pregnancy, with prevalence of drinking returning to high levels in cases and increasing among controls. This replicates a trend reported internationally (Substance Abuse and Mental Health Services Administration, 2009). More encouraging was the fact that cessation in pregnancy was associated with less likelihood of drinking at the time of interview, and may therefore predict reduced drinking in the longer term. Pregnancy may thus be a key opportunity to secure long-term cessation of drinking. This warrants investigation. Despite this, ongoing binge drinking, together with limited use of contraception meant that, when interviewed, 1 in 4 cases and 1 in 12 controls were vulnerable to high-risk AEP.

It is likely that inter-site variations in cessation relate in part to levels of awareness of the risks of drinking in pregnancy. Increasing efforts are being made to educate the public about such risks, especially in urban areas of the Western Cape Province. The fact that the surveys show increasing rates of cessation in the chronological order of the surveys is also consistent with growing awareness over time. A similar temporal trend was also noted in a separate series of FAS prevalence surveys in the Cape Winelands (May et al., 2000, 2007, 2013a; Viljoen et al., 2005). An alternative interpretation is that women more frequently report a reduction in drinking during pregnancy due to growing stigma. We think this is less likely, since our findings are compatible with a previous South African study showing that an awareness-raising intervention can lower rates of P/FAS in infants (Chersich et al., 2012).

In terms of shifts in the volume of alcohol consumed during pregnancy, a small minority of women, especially at WB, increased drinking in pregnancy. Our participants' free text comments support the contention of Watt et al. (2014) that stress and unwanted pregnancy contribute to this: of eight women increasing drinking, five reported being 'very' or 'extremely' stressed during pregnancy. All were farm labourers, which we think is important, because pregnant female farm workers are a particularly vulnerable and disempowered group (Kehler, 2001). Also, although strict enforcement is believed to have eliminated 'Dop' (Gossage et al., 2014), the fact that 'Dop' was previously received by some in the WB site suggests that ongoing vigilance is required.

Smoking prevalence was lower in the later studies, perhaps indicating that public health measures such as increased pricing are having an effect. Infrequent use of other drugs probably relates to alcohol use not being historically linked to drugs in these regions, though this is changing in metropolitan areas (Myers et al., 2014).

The predominantly social pattern of drinking – together with partners, family or friends – is well described in South African settings (London, 1999; Watt et al., 2014). We concur with Watt et al. (2014) that women in this population probably drink to retain social connections, though the quality of these connections is unclear – drinkers were less likely to have a 'best friend'. Few women drank in taverns or other public venues, suggesting that venue-based interventions may have limited impact.

Despite ongoing binge drinking, relatively few perceived this as a problem, reducing the likelihood of change or of entering harm reduction services. There was inter-site variation in levels of concern about drinking, with hardly any SB women perceiving it to be a problem. Women at this site were also more likely to stop drinking in pregnancy, and to restart afterwards. We hypothesize that this pattern is consistent with women being more aware of FAS as a problem, but less concerned about other personal risks of drinking.

Case children were much more likely than controls to have been placed in foster care, or to have spent prolonged periods with relatives. While relatives often play a role in childcare in South Africa, formal placement in foster care was a strong marker for FAS at all sites. This is well described elsewhere (Lange et al., 2013), but has not been evident in previous South African studies, and may reflect improving social services.

The background of low income, unemployment and poor education was common to most case women. The rural WB site showed particularly low educational levels, but higher rates of employment (though often seasonal or part time), which is consistent with the fact that most women at this site were farm labourers (London, 2003). The inland FB site showed relatively higher levels of education and household income, but this income was eroded by larger household size and several markers of deprivation were evidence: more frequent unemployment, informal housing, and high prevalence of BMI in the underweight range.

Control subjects had a mean BMI in the obese range – a finding that is consistent with the rapidly increasing prevalence of obesity in South Africa, particularly among poor, urban females (Kruger et al., 2005). The high prevalence of underweight among cases, especially at the FB site, heightens their vulnerability. It is an independent risk factor for poor pregnancy outcomes (Rahman et al., 2015) and for lower developmental function in children (May et al., 2013b). In addition, body weight affects alcohol metabolism (Khaole et al., 2004) among other morbidities. For these reasons, nutritional interventions may be important for future P/FAS prevention initiatives. This could include state support during pregnancy as provided in a multitude of countries (Murray et al., 2012), enabling women to improve the quantity and quality of their food intake during pregnancy.

4.1. Limitations

Interviewers questioned the reliability of a minority of interviews. However, the proportion of case women who denied using alcohol in pregnancy was somewhat higher than in previous South African studies (May et al., 2005). It is possible that a small proportion of cases were misclassified as P/FAS, or that responses may indicate social desirability bias or recall bias. Recall may be affected by binge drinking, and by the 7–8 year interval between the index pregnancy and the interview, though there is evidence to support the validity of retrospective methods to detect alcohol use (Hannigan et al., 2010).

A control group was only available for one site, but nevertheless provided an important point of comparison. Also, because most available interview data pertained to women in the mixed ancestry

SAC group, and because ethnicity is a determinant of drink-related harm (Chartier et al., 2013), we decided to restrict our focus to this group. Although P/FAS is present in other South African populations (Urban et al., 2015) it is likely that our findings are not generalizable to these groups, because of variation in drinking practices (O'Connor et al., 2014) and other factors affecting alcohol-related harm.

4.2. Conclusions and implications for intervention

This study extends knowledge of maternal drinking practices and risk factors for P/FAS in a high risk South African population: the prevalence of P/FAS was in excess of 5% at all 3 study sites.

Between the time of pregnancy and the interview 7–8 years later, the prevalence of maternal drinking remained high in cases and increased in controls, usually in a weekend binge-drinking pattern. During pregnancy, most controls and some cases stopped drinking, although this did not necessarily prevent P/FAS, perhaps in part due to delayed recognition of pregnancy. Although cessation in pregnancy was often followed by recidivism in the year thereafter, it was associated with lower prevalence of drinking in the longer term.

Given that a significant proportion of high-risk drinkers contemplate stopping or reducing drinking in pregnancy, we recommend that selective interventions target antenatal care, and that early initiation of antenatal care be strongly promoted. However, interventions should continue into the puerperium, encompass a focus on contraception and take into account that most women do not consider their drinking a problem. These features could be incorporated into broader health promotion interventions targeting pregnancy and early childhood, such as the community health worker program being developed in South Africa (Tomlinson et al., 2016).

Conflict of interest

No conflict declared.

Role of funding source

Nothing declared.

Contributors

The work presented in the article was carried out in collaboration between all the authors. MFU, LO, DLV and MFC made substantial contributions to the design of the work. DV, JGL, LO, CL and MFU contributed to the study protocol, procedures, and acquisition of the data. MFU, MFC and FS contributed to the analysis of the data and drafted the manuscript. All authors critically reviewed the final manuscript.

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References

Abel, E.L., Hannigan, J.H., 1995. Maternal risk factors in fetal alcohol syndrome: provocative and permissive influences. Neurotoxicol. Teratol. 17, 445–462, http://dx.doi.org/10.1016/0892-0362(95)98055-6.

Balachova, T., Bonner, B., Chaffin, M., Bard, D., Isurina, G., Tsvetkova, L., Volkova, E., 2011. Women's alcohol consumption and risk for alcohol-exposed pregnancies in Russia. Addiction 107, 109–117.

Balachova, T., Sobell, L.C., Agrawal, S., Isurina, G., Tsvetkova, L., Volkova, E., Bohora, S., 2015. Using a single binge drinking question to identify Russian women at risk for an alcohol-exposed pregnancy. Addict. Behav. 46, 53–57, http://dx.doi.org/10.1016/j.addbeh.2015.03.003.

Centers for Disease Control, 2005. CDC Clinical Growth Charts, Available at: http://www.cdc.gov/growthcharts/ (accessed 30.01.16).

Chartier, K., Vaeth, A.C., Caetano, R., 2013. Focus on: ethnicity and the social and health harms from drinking. Alcohol Res. 35, 229–237.

Chersich, M.F., Urban, M., Olivier, L., Davies, L., Chetty, C., Viljoen, D., 2012. Universal prevention is associated with lower prevalence of fetal alcohol spectrum disorders in Northern Cape, South Africa: a multicentre before-after study. Alcohol 47, 67–74, http://dx.doi.org/10.1093/alcalc/agr145.

Department of Health and Medical Research Council, 2007. South Africa Demographic and Health Survey 2003. Department of Health, Pretoria, Available at: http://www.mrc.ac.za/bod/sadhs.htm (accessed 5.12.15).

Floyd, R.L., Weber, M.K., Denny, C., O'Connor, M.J., 2009. Prevention of fetal alcohol spectrum disorders. Dev. Disabil. Res. Rev. 15, 193–199, http://dx.doi.org/10.1002/ddrr.75.

Fortin, M., Muckle, G., Anassour-Laouan-Sidi, E., Jacobson, S.W., Jacobson, J.L., Bélanger, R.E., 2015. Trajectories of alcohol use and binge drinking among pregnant Inuit women. Alcohol 51, 339–346, http://dx.doi.org/10.1093/alcalc/agv112.

Gossage, J.P., Snell, C., Parry, C.D.H., Marais, A.S., Barnard, R., de Vries, M., Blankenship, J., Seedat, S., Hasken, J.M., May, P.A., 2014. Alcohol use, working conditions, job benefits and the legacy of the Dop system among farm workers in the Western Cape Province, South Africa: hope despite high levels of risky drinking. Int. J. Environ. Res. Public Health 11, 7406–7424, http://dx.doi.org/10.3390/ijerph110707406.

Hannigan, J.H., Chiodo, L.M., Sokol, R.J., Janisse, J., Ager, J., Greenwald, M.K., Delaney-Black, V., 2010. A 14 year retrospective maternal report of alcohol consumption in pregnancy predicts pregnancy and teen outcomes. Alcohol 44, 583–594, http://dx.doi.org/10.1016/j.alcohol.2009.03.003.

Hoyme, H.E., May, P.A., Kalberg, W.O., Kodituwakku, P., Gossage, J.P., Trujillo, P.M., Buckley, D.G., Miller, J.H., Aragon, A.S., Khaole, N., Viljoen, D.L., Jones, K.L., Robinson, L.K., 2005. A practical clinical approach to diagnosis of fetal alcohol spectrum disorders: clarification of the 1996 Institute of Medicine criteria. Pediatrics 115, 39–47, http://dx.doi.org/10.1542/peds.2004-0259.

Kehler, J., 2001. Women and poverty: the South African experience. J. Int. Women's Stud. 3, 41–53.

Khaole, N.C.O., Ramchandani, V.A., Viljoen, D.L., Li, T., 2004. A pilot study of alcohol exposure and pharmacokinetics in women with or without children with fetal alcohol syndrome. Alcohol 39, 503–508, http://dx.doi.org/10.1093/alcalc/agh089.

Kruger, H.S., Puoane, T., Senekal, M., van der Merwe, M., 2005. Obesity in South Africa: challenges for government and health professionals. Public Health Nutr. 8, 491–500, http://dx.doi.org/10.1079/PHN2005785.

Lange, S., Shield, K., Rehm, J., Popova, S., 2013. Prevalence of fetal alcohol spectrum disorders in child care settings: a meta-analysis. Pediatrics 132, 980–995, http://dx.doi.org/10.1542/peds.2013-0066.

London, L., 1999. The dop system, alcohol abuse and social control amongst farm workers in South Africa: a public health challenge. Soc. Sci. Med. 48, 1407–1414, http://dx.doi.org/10.1016/S0277-9536(98)00445-6.

London, L., 2003. Health of farm workers in South Africa. Int. J. Occup. Environ. Health 9, 59–68.

May, P.A., Gossage, J.P., 2011. Maternal risk factors for fetal alcohol spectrum disorders. Alcohol Res. Health 34, 15–26.

May, P.A., Brooke, L., Gossage, J.P., Croxford, J., Adnams, C., Jones, K.L., Robinson, L., Viljoen, D., 2000. Epidemiology of fetal alcohol syndrome in a South African community in the Western Cape Province. Am. J. Public Health 90, 1905–1912, http://dx.doi.org/10.2105/ajph.90.12.1905.

May, P.A., Gossage, J.P., Brooke, L.E., Snell, C.L., Marais, A.S., Hendricks, L.S., Croxford, J.A., Viljoen, D.L., 2005. Maternal risk factors for fetal alcohol syndrome in the Western Cape Province of South Africa: a population-based study. Am. J. Public Health 95, 1190–1199, http://dx.doi.org/10.2105/AJPH.2003.037093.

May, P.A., Gossage, J.P., Marais, A., Adnams, C.M., Hoyme, H.E., Jones, K.L., Robinson, L.K., Khaole, N.C.O., Snell, C., Kalberg, W.O., Hendricks, L., Brooke, L., Stellavato, C., Viljoen, D.L., 2007. The epidemiology of fetal alcohol syndrome and partial FAS in a South African community. Drug Alcohol Depend. 88, 259–271, http://dx.doi.org/10.1016/j.drugalcdep.2006.11.007.

May, P.A., Blankenship, J., Marais, A., Gossage, J.P., Kalberg, W.O., Barnard, R., De Vries, M., Robinson, L.K., Adnams, C.M., Buckley, D., Manning, M., Jones, K.L., Parry, C., Hoyme, H.E., Seedat, S., 2013a. Approaching the prevalence of the full spectrum of fetal alcohol spectrum disorders in a South African population-based study. Alcohol. Clin. Exp. Res. 37, 818–830, http://dx.doi.org/10.1111/acer.12033.

May, P.A., Tabachnick, B.G., Gossage, J.P., Kalberg, W.O., Marais, A., Robinson, L.K., Manning, M.A., Blankenship, J., Buckley, D., Hoyme, H.E., Adnams, C.M., 2013b.

Maternal factors predicting cognitive and behavioral characteristics of children with fetal alcohol spectrum disorders. J. Dev. Behav. Pediatr. 34, 314–325, http://dx.doi.org/10.1097/DBP.0b013e3182905587.
Morojele, N.K., London, L., Olorunju, S.A., Matjila, M.J., Davids, A.S., Rendall-Mkosi, K.M., 2010. Predictors of risk of alcohol-exposed pregnancies among women in an urban and a rural area of South Africa. Soc. Sci. Med. 70, 534–542, http://dx.doi.org/10.1016/j.socscimed.2009.10.040.
Murray, S.F., Hunter, B.M., Bisht, R., Ensor, T., Bick, D., 2012. Demand-side financing measures to increase maternal health service utilisation and improve health outcomes: a systematic review of evidence from low- and middle-income countries. JBI Lib. Syst. Rev. 10 (58), 4165–4567, JBL000592.
Myers, B., Kline, T.L., Doherty, I.A., Carney, T., Wechsberg, W.M., 2014. Perceived need for substance use treatment among young women from disadvantaged communities in Cape Town, South Africa. BMC Psychiatry 14 (100), http://dx.doi.org/10.1186/1471-244x-14-100.
National Institute on Alcoholism and Alcohol Abuse, 2005. Helping Patients Who Drink Too Much: A Clinician's Guide, Updated 2005 Edition, http://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/guide.pdf (accessed 21.08.16).
Nellhaus, G., 1968. Head circumference from birth to eighteen years. Practical composite international and interracial graphs. Pediatrics 41, 106–114.
O'Connor, M.J., Rotheram-Borus, M.J., Tomlinson, M., Bill, C., LeRoux, I.M., Stewart, J., 2014. Screening for fetal alcohol spectrum disorders by nonmedical community workers. J. Popul. Ther. Clin. Pharmacol. 21, 442–452.
Rahman, M.M., Abe, S.K., Kanda, M., Narita, S., Rahman, M.S., Bilano, V., Ota, E., Gilmour, S., Shibuya, K., 2015. Maternal body mass index and risk of birth and maternal health outcomes in low- and middle-income countries: a systematic review and meta-analysis. Obes. Rev. 16, 758–770, http://dx.doi.org/10.1111/obr.12293.
Ramsoomar, L., Morojele, N., 2012. Trends in alcohol prevalence, age of initiation and association with alcohol-related harm among South African youth: implications for policy. S. Afr. Med. J. 102, 609–612.
Rendall-Mkosi, K., Morojele, N., London, L., Moodley, S., Singh, C., Girdler-Brown, B., 2013. A randomized controlled trial of motivational interviewing to prevent risk for an alcohol-exposed pregnancy in the Western Cape, South Africa. Addiction 108, 725–732, http://dx.doi.org/10.1111/add.12081. assessment
Sobell, L.C., Agrawal, S., Annis, H., Ayala-Velasquez, H., Echeverria, L., Leo, G.I., Rybakowski, J.K., Sandahl, C., Saunders, B., Thomas, S., Zioikowski, M., 2001. Cross-cultural evaluation of two drinking instruments: alcohol timeline follow-back and inventory of drinking situations. Subst. Use Misuse 36, 313–331, http://dx.doi.org/10.1081/JA-100102628.
Statistics South Africa, 2012. Census 2011 in Brief. Statistics South Africa, Pretoria.
Substance Abuse and Mental Health Services Administration, 2009. The NSDUH Report: Substance Use Among Women During Pregnancy And Following Childbirth. Office of Applied studies, Rockville, MD.
Tomlinson, M., Rotheram-Borus, M.J., leRoux, I.M., Youssef, M., Nelson, S., Scheffler, A., Weiss, R., O'Connor, M.J., Worthman, C.M., 2016. Thirty-six-month outcomes of a generalist paraprofessional perinatal home visiting intervention in South Africa on maternal health and child health and development. Prev. Sci., http://dx.doi.org/10.1007/s11121-016-0676-x.
Urban, M., Chersich, M.F., Fourie, L., Chetty, C., Olivier, L., Viljoen, D., 2008. Fetal alcohol syndrome among grade 1 schoolchildren in Northern Cape Province: prevalence and risk factors. S. Afr. Med. J. 98, 877–882.
Urban, M.F., Olivier, L., Viljoen, D., Lombard, C., Louw, J.G., Drotsky, L., Temmerman, M., Chersich, M.F., 2015. Prevalence of fetal alcohol syndrome in a South African city with a predominantly black African population. Alcohol. Clin. Exp. Res. 39, 1016–1026, http://dx.doi.org/10.1111/acer.12726.
Viljoen, D., Croxford, J., Gossage, J.P., Kodituwakku, P.W., May, P.A., 2002. Characteristics of mothers of children with fetal alcohol syndrome in the Western Cape Province of South Africa: a case control study. J. Stud. Alcohol 63, 6–17.
Viljoen, D., Craig, P., Hymbaugh, K., Boyle, C., Blount, S., 2003. Fetal alcohol syndrome – South Africa 2001. Morb. Mortal. Wkly. Rep. 52, 660–662.
Viljoen, D., Gossage, J.P., Brooke, L., Adnams, C.M., Jones, K.L., Robinson, L.K., Hoyme, H.E., Snell, C., Khaole, N.C.O., Kodituwakku, P., Asante, K.O., Findlay, R., Quinton, B., Marais, A.S., Kalberg, W.O., May, P.A., 2005. Fetal alcohol syndrome epidemiology in a South African community: a second study of a very high prevalence area. J. Stud. Alcohol 66, 593–604.
Watt, M.H., Eaton, L.A., Choi, K.W., Velloza, J., Kalichman, S.C., Skinner, D., Sikkema, K.J., 2014. It's better for me to drink, at least the stress is going away: perspectives on alcohol use during pregnancy among South African women attending drinking establishments. Soc. Sci. Med. 116, 119–125, http://dx.doi.org/10.1016/j.socscimed.2014.06.048.

4.3 STUDY OF A PREVENTIVE INTERVENTION

4.3.1 STUDY 5

Chersich MF, **Urban M**, Olivier L, Davies L, Chetty C, Viljoen D. Universal prevention is associated with lower prevalence of fetal alcohol spectrum disorder in Northern Cape, South Africa: a multicentre before-after study. Alcohol Alcohol 2012; 47(1):67-74.

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ORIGINAL ARTICLE

Universal Prevention is Associated with Lower Prevalence of Fetal Alcohol Spectrum Disorders in Northern Cape, South Africa: A Multicentre Before–After Study

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Abstract — Aims: Prevalence of fetal alcohol spectrum disorders (FASDs) is remarkably high in several provinces of South Africa; yet population-level knowledge of the harms of maternal drinking remains low. In two heavily affected areas, we assessed effectiveness of interventions to heighten awareness of these harms and to alter social norms about drinking in pregnancy. **Methods:** FASD prevalence, maternal knowledge and drinking behaviours were investigated in two Northern Cape Province towns, before and after interventions which included highlighting FASD using local media and health promotion talks at health facilities. Independently, two dysmorphologists and a neuropsychometrist examined children at 9 and 18 months. **Results:** Pre-intervention maternal knowledge of alcohol harms was low and FASD prevalence 8.9% (72/809). Interventions reached high coverage and knowledge levels increased substantially. FASD prevalence was 5.7% post-intervention (43/751; $P = 0.02$); 0.73 lower odds, controlling for maternal age and ethnicity (95% confidence interval = 0.58–0.90). No change was detected in more severe FASD forms, but in the whole population, median dysmorphology scores reduced from 4 [inter-quartile range (IQR) = 2–7] to 3 (IQR = 1–6; $P = 0.002$). **Conclusion:** This, the first prevention study using FASD outcomes, suggests that universal prevention might reduce FASD by ~30% and have population-level effects. This supports intensifying universal interventions where knowledge of harms of maternal drinking is low. These efforts need to be accompanied by alcohol-dependence treatment to lower more severe FASD forms.

INTRODUCTION

Fetal alcohol spectrum disorder (FASD) is among the commonest causes of learning disability worldwide, and is eminently preventable (American Academy of Pediatrics, 2000). Globally, some of the highest rates occur in South Africa, and while no systematic surveillance system is in place, several studies suggest levels are increasing (May *et al*., 2000; Urban *et al*., 2008). In the late 1990s, a study in Wellington in the Western Cape Province reported a prevalence of FASD of 40.5–46.6 per 1000 children 5–9 years (May *et al*., 2000). Two subsequent surveys in the same area, using similar methods reported even higher levels of between 65.2–74.2 per 1000 children in 2000 (Viljoen *et al*., 2005) and then 68.0–89.2 per 1000 children in 2002 (May *et al*., 2007). Between 2001 and 2004, among the highest ever reported FASD rates were found in school-entry children in two towns in the Northern Cape Province, De Aar (119.4/1000) and Upington (74.7/1000) (Urban *et al*., 2008). Clearly, South Africa has a massive and even increasing FASD burden.

The most common drinking pattern in pregnant women that results in FASD is heavy-episodic (binge) drinking. This drinking pattern, common among women in many parts of South Africa (Peltzer and Ramlagan, 2009; Ojo *et al*., 2010), is amenable to intervention, as it is not necessarily associated with alcohol dependence (WHO, 2001a). Universal approaches to FASD prevention aim to increase population-level understanding of the harms of alcohol use in pregnancy and thereby shift drinking norms. In indicated prevention, high-risk individuals receive interventions, such as women with alcohol dependence or those who already have a child with FASD (Astley *et al*., 2000). Most FASD prevention studies to date have tested a third prevention modality, selective interventions. This often involves screening pregnant women for alcohol use and then providing, for example, brief interventions for those at high risk (Stratton K *et al*., 1996; Hankin, 2002, Centers for Diseases Control and Prevention 2009; Floyd *et al*., 2009). A systematic review identified only four FASD prevention trials, which together suggested that brief psychological and educational interventions may reduce alcohol use among pregnant women (Stade *et al*., 2009). No studies had FASD diagnosis as a study endpoint.

This study assessed whether FASD prevalence would be reduced by universal interventions to raise community and health worker awareness of the harms of maternal drinking and to shift-related social norms. Changes in FASD prevalence, and in maternal knowledge and drinking behaviour, were assessed in two small South African towns before and after interventions provided mainly by community workers and through the local media.

MATERIALS AND METHODS

The study was conducted in De Aar and Upington, towns in the arid Northern Cape Province, populated predominately by people of mixed ancestry. Both towns have high indices of socio-economic deprivation (Bureau of Census, 2001). De Aar is a railway and sheep farming centre with about 28,000 inhabitants, whereas Upington is a viticulture area of 58,000 people on the banks of the Orange River. The study took place from 2003 to 2006 in De Aar and from 2005 to 2010

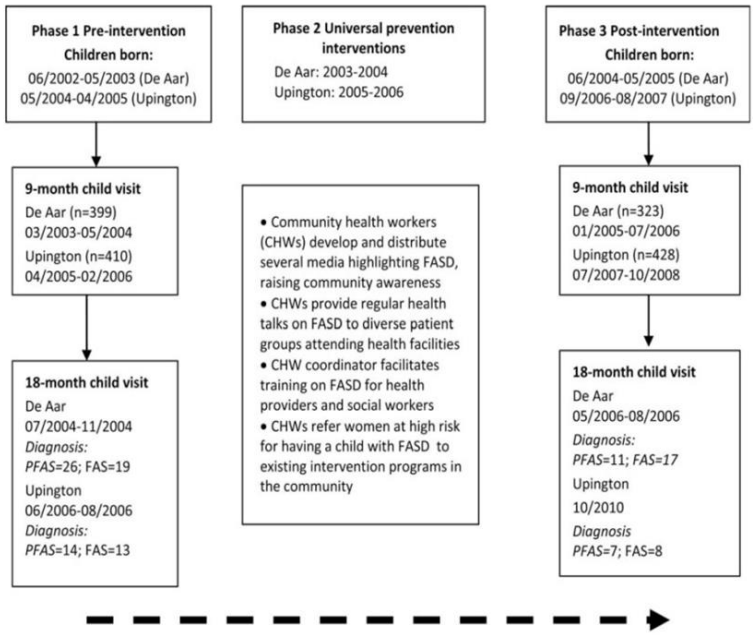

Fig. 1. Flowchart of the three study phases of the FASDs prevention study.

in Upington (Fig. 1). There were three study phases: firstly, a baseline assessment of fetal alcohol syndrome (FAS) and partial FAS (PFAS) prevalence; secondly, prevention interventions; and, finally, 1 year thereafter, assessment of FAS/PFAS prevalence (Fig. 1).

Before and after the prevention intervention, cohorts of infants, born in a 1-year period, were identified through birth records collected from public-sector hospitals. In both phase one and three in De Aar, we attempted to trace all children born in each 1-year period. As Upington has a larger population, in both phase one and three, a random sample of about half the children was selected from a list of all births in each 1-year period. A random number table was used in this selection. In both sites, community-health workers (CHWs) used contact information from birth records to trace the infants' mothers or guardians (if the mother was unavailable or deceased). Women who had moved from the area between childbirth and the time of the interview were excluded.

Phase one and three: assessing study outcomes before and after intervention

Identical procedures were used in phases one and three. Birth weight was obtained from hospital records, and maternal age, ethnicity and infant anthropometry were collected from participants at the 9-month visit. Infant length was measured using rubber Measure Mats. A structured questionnaire, previously developed and tested in the local population (Viljoen DL *et al.*, 2003), was administered by a trained counsellor or neuropsychometrist to mothers. Guardians completed abbreviated proxy interviews. Interviews measured demographics, socio-economic exposures and alcohol use in FAS/PFAS cases and an equal number of controls, matched for ethnicity and infant age. Beck's Depression Inventory was used to screen for maternal depression (Beck *et al.*, 1961; Ward *et al.*, 2003). We assessed alcohol use in the period around the time of the interview and during pregnancy using a timeline follow-back method (Sobell *et al.*, 2001). Maternal knowledge and attitudes to alcohol use, and the amount of exposure to the intervention were also assessed.

Infants were examined for dysmorphic features and neurological signs at 9 months and those with evidence of FAS/PFAS were re-examined at 18 months, alongside control infants. To standardize assessment of dysmorphic features, a checklist (May *et al.*, 2000) was used to yield a dysmorphology score, with a maximum score of 35. All infants were evaluated independently by two trained clinicians, skilled in diagnosing FAS/PFAS. Infants with features suggesting FAS/PFAS and control infants had a developmental assessment using the Griffiths Mental Development Scale (Griffiths R, 1970), validated in some South African

populations (Adnams *et al*., 2001). Development was evaluated over the following modalities: locomotor; personal-social; hearing and speech; eye-hand coordination; skills in manipulation and speed of performance and executive functioning. Subscale quotients for each skill area were derived independently, and a general developmental quotient obtained by combining the subscale scores. If developmental indices could not be determined due to very low test scores, an index score of 50 was assigned. For FAS/PFAS diagnostic purposes, infants were classified as having neurocognitive delay if any of the subscales were ≤68 (2 standard deviations below the expected mean of 100), or the general developmental total score was ≤84 (1 standard deviation below expected mean) (Griffiths R, 1970).

A FAS diagnosis was made when infants had the characteristic facial phenotype (including small palpebral fissures, midface hypoplasia, smooth philtrum and thin vermilion border); growth deficiency (≤10th percentile for height, weight or head circumference) and documentation of central nervous system abnormalities (Hoyme *et al*., 2005). Clinical diagnoses of FAS, but not PFAS, are considered distinctive even in the absence of a history of maternal alcohol consumption in pregnancy (National Center on Birth Defects and Developmental Disabilities *et al*., 2004; Hoyme *et al*., 2005). In addition to confirmation of maternal drinking, a PFAS diagnosis also required at least two of the three characteristic FAS facial features and one of growth retardation, neurological abnormality or abnormal neurocognitive assessment (Hoyme *et al*., 2005). Only FAS/PFAS cases were assessed, in particular cases of alcohol-related neurodevelopmental disorder (ARND) were not ascertained, as the more subtle neurological features of this disorder are harder to detect in infancy. Final diagnoses were made in a case conference, reviewing all available data. For analysis purposes, FAS and PFAS cases were combined, forming the FAS/PFAS group.

Phase two: universal FASD prevention interventions

At baseline, prior to the prevention activities, coverage of interventions to educate women about the harms of drinking during pregnancy was relatively low. Only 39.5% (30/76) of cases and controls recalled having received information about FASD on the radio or television, while about two-thirds reported receiving this information from a nurse. In phase two, FASD prevention activities were provided using multiple platforms, over 1 year. Three trained CHWs led activities in each site. They received a monthly stipend and were supervised by full-time study coordinators (professional nurses). With input from local community representatives, a pamphlet and poster were designed and distributed to antenatal clinics, shops, taverns, government departments and prisons. Regular articles focusing on FASD prevention, and emphasizing the responsibility of both parents and the community for its prevention, were published in local community newspapers and reinforced by regular advertisements on the local community radio. Local drama productions on FASD themes were performed.

Community workers presented 'health talks' at clinics for infants and young children, family planning and antenatal care and at church and community meetings. These addressed a range of topics such as nutrition, breastfeeding and family spacing, but were always underscored by messaging on FASD prevention. Training workshops on FASD were held for provincial and district-level staff from the Departments of Health and Social Services. FASD prevention messages were mainstreamed within the Department of Health's activities and in their interactions with the public, with FASD topics given prominence in all National Health Promotion events, such as Women's Day, Pregnancy Education Week, International FASD Day and Breast Cancer Awareness Month.

Study measures and analysis

Single data entry was done in a Microsoft Access 2003 (Microsoft, Redmond, WA, USA) database, and Intercooled Stata version 10.1 (Stata-Corp, LP, College Station, TX, USA) used for analysis. Prevalence of study outcomes was compared before and after the intervention. The primary outcome was FAS/PFAS prevalence. Secondary outcomes were: maternal knowledge about harms of alcohol use during pregnancy; self-report of maternal alcohol consumption; birth weight; infant anthropometry; neurodevelopment subscales and dysmorphology scores. As there were few white or Asian participants, these groups were combined with Black-Africans and outcomes in this group compared with people of mixed ancestry (79.1% of the population).

The χ^2 test detected differences between categorical variables, and a χ^2 test for trend assessed whether there was an increasing trend in proportions over exposure categories. For continuous variables, an unpaired Student's *t*-test or Mann–Whitney *U*-test compared data with a normal and non-normal distribution respectively. Infant anthropometric data were analysed using *z*-scores computed with the WHO Child Growth Standards program in Stata (WHO Anthro. Child Growth Standards). Multivariate logistic regression models investigated whether study phase was associated with FAS/PFAS diagnosis, controlling for maternal age, ethnicity and study site. As other socio-demographic data were only collected in a population subset (PFAS/FAS cases and controls) these variables were not included in multivariate models.

Ethical considerations

Study activities were approved by the University of Witwatersrand Human Research Ethics Committee. Informed consent was obtained from the mothers or guardians willing to participate. Throughout the study, women showing signs of alcohol dependence or children diagnosed with FASD were linked with a local alcohol treatment centre and the Department of Social Services. Assistance was offered in accessing government welfare grants, where applicable. The study team also provided some support for women with alcohol dependence or children with FASD through, for example, creating a toy library and play group, aimed at promoting early childhood development and maternal bonding. Women diagnosed with depression, an important FASD risk factor (Meschke *et al*., 2003; Parker *et al*., 2010), were referred for treatment and to local support groups. Children with FASD were linked with speech and hearing therapists, and occupational therapists. Malnourished children were referred to a dietician and enrolled into a local protein-energy malnutrition program.

RESULTS

In the pre-intervention phase, 809 children were enrolled (399 in De Aar and 410 in Upington), and 751 participated post-intervention (323 and 428 in the corresponding towns). Of the 500 births in the past year in De Aar phase one, 399 infants were located and enrolled (79.8%). Participation rates were very similar in Upington phase three—428 enrolled of the 538 birth records selected. Participation information is not available for De Aar phase three and Upington phase one. Field workers reported that very few women located declined to participate, non-participation was predominately due to women having moved or addresses in the birth records being incorrect or incomplete. At first examination, children were a median 10.5 months [inter-quartile range (IQR) = 9.7–11.4], and an average 2.5 weeks older in the post-intervention group (Table 1). Slightly more than half the infants were female (50.5%), while 57.4% of FAS/PFAS infants were female. Maternal age at the time of the 9-month visit was similar in each phase, an overall mean 27.2 years (sd = 6.6), with 13.5% aged above 35 years (195/1444). The majority of women were of mixed ancestry (79.1%, 1186/1500), with the remainder mostly black (19.0%, 285/1500). Among cases and controls, three-quarters of pregnancies were unplanned (124/167), similar in phases one and three. No change was detected in unemployment levels between the phases.

The 84.0% of cases and controls who ever drank alcohol (158/188), recalled having their first drink at a mean 18.6 years (sd = 3.8). Alcohol debut was similar between phases, and in FAS/PFAS and non-FAS/PFAS cases, but was earlier in De Aar (17.7 years) than Upington (20.3 years; $P < 0.001$). Prior to the study intervention, only about half the cases and controls were aware that drinking in pregnancy could harm the fetus.

Table 1. Socio-demographic characteristics of women and infants before and after an intervention to reduce FASDs in Northern Cape, South Africa

Variable	Before intervention (A)	After intervention (B)	*P* (A vs. B)	FAS/PFAS cases before intervention (C)	FAS/PFAS cases after intervention (D)	*P* (C vs. D)
Whole study population in both sites						
Infant age at examination[a] median months (IQR), *n*	10.2 (9.5–11.0), 801	10.8 (9.9–12.0), 720	<0.001	10.4 (9.3–11.1), 72	11.2 (9.7–13.0), 42	0.01
Infant gender *n* female/*N* (%)	413/793 (52.1)	357/730 (48.9)	0.22	40/72 (56)	26/43 (61)	0.61
Maternal age[b] mean years (sd), *n*	27.2 (6.4), 769	27.4 (6.8), 677	0.62	32.3 (5.8), 68	33.0 (6.2), 35	0.54
Ethnicity *n*/*N* (%)						
Mixed ancestry	608/776 (78.4)	578/724 (79.8)	0.48	66/72 (92)	41/43 (95)	0.45
Black, Asian and whites	168/776 (21.7)	146/724 (20.2)		6/72 (8)	2/43 (5)	
Cases and controls in both sites						
Marital status *n*/*N* (%)[c]						
Single	81/127 (63.8)	47/65 (72.3)	0.49	40/69 (58)	21/34 (62)	0.81
Married/engaged	26/127 (20.5)	10/65 (15.4)		13/69 (19)	7/34 (21)	
Living together	20/127 (15.8)	8/65 (12.3)		16/69 (23)	6/34 (18)	
Parity *n*/*N* (%)[c]						
1	28/126 (22.2)	14/64 (21.9)	0.96	7/69 (10)	5/33 (15)	0.57
2	39/126 (31.0)	19/64 (29.7)		18/69 (26)	8/33 (24)	
3	24/126 (19.1)	11/64 (17.2)		18/69 (26)	5/33 (15)	
≥4	35/126 (27.8)	20/64 (31.3)		26/69 (38)	15/33 (45)	
Highest education *n*/*N* (%)[c]						
None or primary incomplete	32/121 (26.5)	18/63 (28.6)	0.87	24/62 (39)	14/32 (44)	0.66
Primary complete	16/121 (13.2)	6/63 (9.5)		11/62 (18)	3/32 (9)	
Secondary incomplete	56/121 (46.3)	29/63 (46.0)		25/62 (40)	13/32 (41)	
Secondary complete	16/121 (13.2)	10/63 (15.9)		2/62 (3)	2/32 (6)	
Tertiary	1/121 (0.8)	0/63 (0.0)		0/62 (0)	0/32 (0)	
Employment *n*/*N* (%)[c]						
Unemployed	106/125 (84.8)	47/61 (77.1)	0.42	57/67 (85)	25/32 (78)	0.61
Temporary worker	10/125 (8.0)	8/61 (13.1)		6/67 (9)	5/32 (16)	
Full time employed	9/125 (7.2)	6/61 (9.8)		4/67 (6)	2/32 (6)	
Maternal depression *n*/*N* (%)[c]						
None	33/117 (28.2)	11/55 (20.0)	0.5	18/62 (29)	3/29 (10)	0.04
Mild depression	22/117 (18.8)	8/55 (14.6)		9/62 (15)	2/29 (7)	
Clinical depression	22/117 (18.8)	11/55 (20.0)		8/62 (13)	7/29 (24)	
Moderate depression	25/117 (21.4)	18/55 (32.7)		13/62 (21)	13/29 (45)	
Severe depression	15/117 (12.8)	7/55 (12.7)		14/62 (23)	4/29 (14)	
Tobacco use during pregnancy *n*/*N* (%)[c]	69/124 (55.7)	34/63 (54.0)	0.83	49/64 (77)	23/33 (70)	0.46

Data from whole study population and χ^2 test used unless indicated.
FAS, fetal alcohol syndrome; PFAS, partial fetal alcohol syndrome; IQR, inter-quartile range; sd, standard deviation.
[a]Mann–Whitney *U*-test.
[b]Student's *t*-test.
[c]Data on cases and controls, not the whole population.

Outcomes before and after study intervention

At baseline, FAS/PFAS prevalence was 8.9% (72/809) and 5.7% post-intervention (43/751, $P = 0.02$; Table 2). The largest change between the phases was a halving of PFAS prevalence (4.9%, 40/809 to 2.4%, 18/751; $P = 0.008$). In multivariate analysis, controlling for maternal age, ethnicity and study site, odds of FAS/PFAS was 0.73 lower in phase three than one [95% confidence interval (CI) adjusted odd ratio (AOR) = 0.58–0.91; Table 3]. Dysmorphology scores of the whole study population were lower in phase three (median score of 4 in phase one, IQR = 2–7; versus 3 in phase three, IQR = 1–6; $P = 0.002$). No difference in infant head circumference was noted between all infants in phase one and three, while comparisons of infant weight (higher in phase three) and length (higher in phase one) yielded divergent findings.

Few differences between the phases were detected in the outcomes measured only in the cases and controls. FAS/PFAS mothers pre-intervention reported drinking a median of 14.9 units a week during pregnancy (IQR = 4.7–31.4), compared with 5.8 median units/week in FAS/PFAS mothers post-intervention (IQR = 3.0–13.2; $P = 0.04$). Changes in volume drunk were, however, only detected in the PFAS group (17.6 median units/week in phase one versus 7.2 units/week in phase three; $P = 0.05$) and not in volumes among women with a FAS child (7.8 median units/week in phase 1 and 4.4 median units/week in phase 3; $P = 0.44$). In the first phase, about half of women who drank in pregnancy reported changing the amount they drank during pregnancy (31/63), and 60% reported this in phase three (24/40; P = 0.36). No difference between phases was detected in neurodevelopment measured in the infant cases and controls. Among FAS/PFAS cases in phase three, levels of moderate or severe depression were higher than among cases in phase one.

The intervention reached a large proportion of the population who recalled receiving information about FASD from nurses (81.3%, 52/64) and the media (60.7%, 34/56). Levels of maternal awareness about alcohol harms increased, with odds of correct knowledge 5.8–10.3 higher in phase three than phase one. When changes in awareness were examined separately by town, differences were detected in all these measures in De Aar, but few were detected in Upington, though all changes were in the same direction of effect. Some changes were detected in drinking attitudes and the giving of alcohol to children. Importantly, 74% (83/112) of women believed that using posters to communicate information about drinking harms could modify women's drinking.

Table 2. Association between infant and maternal characteristics before and after a universal FASD prevention intervention in Northern Cape, South Africa

Variable group	Category (%)	Before intervention	After intervention	*P*-value
Infant outcomes in whole population				
FAS/PFAS	No FAS/PFAS	737/809 (91.1)	708/751 (94.3)	0.02
	PFAS	40/809 (4.9)	18/751 (2.4)	
	FAS	32/809 (4.0)	25/751 (3.3)	
Dysmorphology	All participants: median score (IQR), *n*	4 (2–7), 809	3 (1–6), 751	0.002[a]
	FAS/PFAS: median score (IQR), *n*	13 (10–16), 72	14 (11–17), 43	0.31[a]
Birth weight	Mean kilogram (sd), *n*	2.9 (0.55), 685	2.9 (0.54), 643	0.89[b]
Infant anthropometry Z scores for age, median (IQR), *n*	Weight	−0.84 (−1.75 to −0.03) 779	−0.57 (−1.47 to −0.27) 711	<0.001[a]
	Weight for length	−0.44 (−1.31 to 0.21) 778	0.06 (−0.87 to 0.87) 710	<0.001[a]
	Length	−0.80 (−1.76 to −0.06) 783	−1.18 (−2.05 to −0.3) 712	<0.001[a]
	Head circumference	0.2 (−0.57 to 0.88) 783	0.2 (−0.49 to 0.95) 712	0.40[a]
Neurodevelopment in cases and controls				
Neuro-development[c]	Mental retardation or borderline (0–84)	22/125 (17.6)	13/55 (23.6)	0.40
	Below average (85–89)	13/125 (10.4)	7/55 (12.7)	
	Average (90–109)	71/125 (56.8)	23/55 (41.8)	
	Above average (110–119)	12/125 (9.6)	9/55 (16.4)	
	Superior (≥120)	7/125 (5.6)	3/55 (5.5)	
Maternal outcomes in cases and controls				
Alcohol use in pregnancy[c]	Never	48/106 (45.3)	23/57 (40.4)	0.39
	1 week each month of pregnancy	10/106 (9.4)	7/57 (12.3)	
	2–3 weeks each month of pregnancy	16/106 (15.1)	14/57 (24.6)	
	Every week in pregnancy	32/106 (30.2)	13/57 (22.8)	
	Median units/week (IQR), *n*	12.1 (4.4–26.5), 55	8.5 (4.4–16.0), 30	0.32
Knowledge about harms of drinking in pregnancy[c]	One drink in pregnancy harms fetus	57/106 (53.8)	60/65 (92.3)	<0.001
	Five drinks on one occasion in pregnancy harms fetus	57/105 (54.3)	57/63 (90.5)	<0.001
	Fine drinks everyday in pregnancy harms fetus	54/104 (51.9)	56/65 (86.2)	<0.001
Alcohol and children[c]	Gives the child alcohol to drink	10/103 (9.7)	2/65 (3.1)	0.10
Study intervention in cases and controls				
Exposure to FASD information[c]	Information from nurses	78/117 (66.7)	52/64 (81.3)	0.04
	Information from radio or TV	30/76 (39.5)	34/56 (60.7)	0.02
Perceptions of drinking modifiability[c]	Posters of harms of drinking during pregnancy would alter alcohol use	43/66 (65.2)	40/46 (87.0)	0.01

Data are *n*/N (%) and χ^2 test unless indicated.
IQR, inter-quartile range; FASD, fetal alcohol spectrum disorder; FAS, fetal alcohol syndrome; PFAS, partial fetal alcohol syndrome.
[a]Mann–Whitney *U*-test.
[b]Student's *t*-test.
[c]Data on cases and controls, not the whole population.

Table 3. Multivariate logistic regression of factors associated with FASDs in Northern Cape, South Africa

Study variable	Univariate odds of FAS/PFAS (95% CI)	Adjusted odds of FAS/PFAS (95% CI)
Study phase		
Before intervention	1	1
After intervention	0.62 (0.42–0.92)	0.73 (0.58–0.91)
Site		
Upington	1	1
De Aar	2.13 (1.44–3.17)	2.40 (1.54–3.74)
Maternal age (years)		
15–19	1	1
20–24	0.85 (0.25–2.86)	0.79 (0.23–2.67)
25–29	2.57 (0.85–7.75)	2.42 (0.80–7.33)
30–34	6.83 (2.34–19.89)	6.26 (2.17–18.03)
35–60	10.36 (3.46–30.98)	11.04 (3.79–32.16)
Ethnicity		
Black or other	1	1
Mixed ancestry	3.79 (1.82–7.90)	4.05 (1.91–8.63)

FAS/PFAS, fetal alcohol syndrome and partial fetal alcohol syndrome; CI, confidence interval.

No change, however, was noted in tobacco use during pregnancy, which remained above 50% in both phases.

Factors associated with FAS/PFAS

Maternal characteristics of children with FAS/PFAS are markedly different from that of the whole population (Table 1, comparing columns A and B with C and D). Most notably, in FAS/PFAS cases, maternal age and parity are substantially higher; women were more likely to be single or cohabiting; maternal educational attainment was lower and two-thirds of these mothers are affected by depression (59/91, 65%). Of 103 FAS/PFAS cases, 36 mothers were aged above 35 years and a further 37 were 30–34 years; together 70.9% of all FAS/PFAS cases were born to women above 30. In multivariate analysis, a stepwise increase in odds of FAS/PFAS was noted with each 5-year increase in age category beyond 25 years. Women of mixed ancestry were 4.05-fold more likely to have a FAS/PFAS child than other women (95%CI AOR = 1.91–8.63). Finally, FAS/PFAS was 2.4 times more likely in De Aar than in Upington (95% CI AOR = 1.54–3.74).

DISCUSSION

Although it is generally recommended that programs to prevent FASD should include universal or community-level measures (Floyd *et al.*, 2009), little has been done to document their effectiveness. The study, albeit in the absence of external controls, found a reduction in FAS/PFAS following CHW-led community- and facility-level interventions to shift drinking norms. Women in phase three had a higher knowledge of the harms of alcohol in pregnancy, and most had been exposed to FASD educational media and believed that these would modify their drinking behaviours. Taken together, these findings provide supportive evidence of the need for enhanced community-level interventions in settings where levels of knowledge about the harms of maternal drinking are low. Further, operationally, CHWs, working with supervision, appear to be effective mediators for such interventions. Levels of FASD pre-intervention (112.8/1000 in De Aar and 65.9/1000 in Upington) were broadly comparable to a previous survey of school-entry children (119.4/1000 in De Aar and 74.7/1000 in Upington). Slight differences between these levels might be ascribed to reduced ability to detect neurobehavioral manifestations of FASD in young children. Though FASD was substantially lower in the post-intervention cohorts, levels remain unacceptably high.

There are few FASD prevention trials to date and the limited data mainly concerns selective interventions during pregnancy (Stade *et al.*, 2009). The study findings, however, concur with overall evidence of the effectiveness of alcohol-reduction interventions. There is much evidence that brief educational or motivational interventions are effective in reducing risky drinking (Moyer *et al.*, 2002; Kaner *et al.*, 2007), across a range of settings (including primary or antenatal health care). Even minimal interventions, such as those provided to control groups in randomized trials, may substantially reduce alcohol consumption (Aalto *et al.*, 2000; O'Connor and Whaley, 2007). We contend that our finding of an association between universal interventions and reduced FASD levels is consistent with this evidence of the modifiability of drinking, even through limited interventions.

Diagnosis of FAS/PFAS is multifaceted and the FAS phenotype evolves over time (Gibbard *et al.*, 2003; National Center on Birth Defects and Developmental Disabilities *et al.*, 2004; Davies L *et al.*, 2011). FASD surveys in South Africa have frequently targeted school-entry children, since the diagnosis is believed to be most easily and accurately made at this age. Nevertheless, FASD guidelines provide for the diagnosis to be made from early in life (Hoyme *et al.*, 2005), which enables early entry of affected children into services to improve their neurodevelopment (Bertrand, 2009) and also allows timely evaluation of outcomes of FASD prevention studies. The early diagnosis of FASD does, however, make it difficult to detect more subtle neurological manifestations of FASD, such as ARND.

A randomised trial among heavy-drinking women reported birth outcomes (weight, length and head circumference) (O'Connor and Whaley, 2007). That trial found that women allocated to a brief intervention had newborns of greater length and birth weight than controls. In our study among the general population, we did not find consistent population-level differences in infant anthropometry, but did detect population-level differences in dysmorphology scores.

The finding that PFAS levels and the volume of alcohol drunk among women with a PFAS infant had decreased to a greater extent than with FAS may be explained by an inability of universal interventions to modify drinking behaviours in women with entrenched heavy drinking or alcohol dependence. Similarly, these interventions may be less effective in women with depression. While universal interventions are well suited to altering occasional episodic drinking in pregnancy, alcohol-dependent women and those with depression require more individualized and specialized services to alter their drinking (WHO, 2001b).

Presently there are initiatives to enhance the role of CHWs in South Africa (Clarke M *et al.*, 2008). There are, however,

challenges in translating CHW-led interventions from research to routine practice environments (Lehmann and Sanders, 2007; Clarke M *et al*., 2008), and within routine services CHWs would require ongoing supervision and monitoring, as in this study. The study also found that nurses were an important source of information regarding FASD, and the most frequently quoted source of information. This is important given that low levels of FASD knowledge among health providers remains a persistent problem globally (National Center on Birth Defects and Developmental Disabilities *et al*., 2004; Brems *et al*., 2010).

Aside from exposure to the study intervention, several other variables were strongly associated with FAS/PFAS occurrence, and similar to the previously identified factors (Morojele *et al*., 2010). Identification of risk factors allows for future studies of selective interventions that target high-risk groups. For example, FAS/PFAS occurred in a fifth of children born to women of mixed ancestry and above 35 years.

Study strengths and limitations

The study is strengthened by having clinical outcome criteria such as FAS/PFAS and population-level dysmorphology scores rather than proxy criteria, as in previous studies. Measures of self-reported drinking likely incurred substantial social-desirability bias, especially post-intervention when awareness of the harms of maternal drinking increased. The study design makes it difficult to attribute the reduction in FAS/PFAS prevalence to the intervention alone, as concurrent changes in the community might account for these effects, even in part. However, the lack of change in tobacco use and employment status, as well as evidence of an increase in FASD in South Africa (discussed in introduction) suggest that temporal changes do not account for all the effects noted in this study. National programs for reducing alcohol use are poorly developed in South Africa and are unlikely to have interfered with our intervention. A more robust experimental study design was deemed unfeasible given the limited study resources available. Nevertheless, the weak design limits the ability to draw firm inferences. Further, collecting information on only the mothers of controls and cases reduced the ability to detect differences between women's behaviours in phases one and three. The absence of data on the participation rates for two of the four cohorts should be noted, this information is important for judging the likelihood of selection bias. Data are also missing for other study variables, mostly due to incomplete information in the multiple data sources used.

Effectiveness of the interventions may be reduced within larger or more transient populations, or where knowledge about the harms of drinking during pregnancy is already high. Low FASD knowledge levels have, however, been documented in several other South African settings (May *et al*., 2005, 2008; Morojele *et al*., 2006).

CONCLUSIONS

This study provides information about the effectiveness of universal prevention of FASD in two South African towns, and suggests that in these and similar communities, concerted efforts to increase awareness about the harms of drinking during pregnancy might lower FASD prevalence. However, even after the intervention, FASD prevalence is extraordinarily high, similar to that of paediatric human immunodeficiency virus infection levels in South Africa; a condition that elicits a markedly higher, yet appropriate, preventive response. Poor socio-economic indicators and frequent unintended pregnancies make intersectoral or structural interventions necessary. In the meantime, markedly increased efforts are needed to alter community norms about drinking in pregnancy, together with selective interventions for high-risk women and alcohol treatment services for women with alcohol dependence.

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REFERENCES

Aalto M, Saksanen R, Laine P *et al*. (2000) Brief intervention for female heavy drinkers in routine general practice: a 3-year randomized, controlled study. *Alcohol Clin Exp Res* **24**:1680–6.

Adnams CM, Kodituwakku PW, Hay A *et al*. (2001) Patterns of cognitive-motor development in children with fetal alcohol syndrome from a community in South Africa. *Alcohol Clin Exp Res* **25**:557–62.

American Academy of Pediatrics (2000) Committee on Substance Abuse and Committee on Children with Disabilities. Fetal alcohol syndrome and alcohol-related neurodevelopmental disorders. *Pediatrics* **106**:358–61.

Astley SJ, Bailey D, Talbot C *et al*. (2000) Fetal alcohol syndrome (FAS) primary prevention through fas diagnosis: II. A comprehensive profile of 80 birth mothers of children with FAS. *Alcohol Alcohol* **35**:509–19.

Beck AT, Ward CH, Mendelson M *et al*. (1961) An inventory for measuring depression. *Arch Gen Psychiatry* **4**:561–71.

Bertrand J. (2009) Interventions for children with fetal alcohol spectrum disorders (FASDs): overview of findings for five innovative research projects. *Res Dev Disabil* **30**:986–1006.

Brems C, Boschma-Wynn RV, Dewane SL *et al*. (2010) Training needs of healthcare providers related to centers for disease control and prevention core competencies for fetal alcohol spectrum disorders. *J Popul Ther Clin Pharmacol* **17**:e405–17.

Bureau of Census (2001) *Census of the Population*. Statistics South Africa: Pretoria, South Africa.

Centers for Diseases Control and Prevention (2009) Alcohol use among pregnant and nonpregnant women of childbearing age—United States, 1991–2005. *Morb Mortal Wkly Rep* **58**:529–32.

Clarke M, Dick J, Lewin S. (2008) Community health workers in South Africa: where in this maze do we find ourselves. *S Afr Med J* **98**:680–1.

Davies L, Dunn M, Chersich M *et al*. (2011) Developmental delay of infants and young children with and without fetal alcohol spectrum disorder in the Northern Cape Province, South Africa. *Afr J Psychiatry* **14**:298–305.

Floyd RL, Weber MK, Denny C *et al*. (2009) Prevention of fetal alcohol spectrum disorders. *Dev Disabil Res Rev* **15**:193–9.

Gibbard WB, Wass P, Clarke ME. (2003) The neuropsychological implications of prenatal alcohol exposure. *Can Child Adolesc Psychiatr Rev* **12**:72–6.

Griffiths R. (1970) *The Ability of Young Children: A Comprehensive System of Mental Measurement for the First Eight Years of Life*. Amersham Bucks, England: The Test Agency, Ltd.

Hankin JR. (2002) Fetal alcohol syndrome prevention research. *Alcohol Res Health* **26**:58–65.

Hoyme HE, May PA, Kalberg WO *et al*. (2005) A practical clinical approach to diagnosis of fetal alcohol spectrum disorders: clarification of the 1996 institute of medicine criteria. *Pediatrics* **115**:39–47.

Kaner EF, Beyer F, Dickinson HO *et al*. (2007) Effectiveness of brief alcohol interventions in primary care populations. *Cochrane Database Syst Rev*: CD004148, 1–65.

Lehmann U, Sanders D. (2007) Community health workers: what do we know about them? Evidence Report for WHO. Available: http://www.hrhresourcecenter.org/node/1587.

May PA, Brooke L, Gossage JP *et al*. (2000) Epidemiology of fetal alcohol syndrome in a South African community in the Western Cape Province. *Am J Public Health* **90**:1905–12.

May PA, Gossage JP, Brooke LE *et al*. (2005) Maternal risk factors for fetal alcohol syndrome in the Western cape province of South Africa: a population-based study. *Am J Public Health* **95**:1190–9.

May PA, Gossage JP, Marais AS *et al*. (2007) The epidemiology of fetal alcohol syndrome and partial FAS in a South African community. *Drug Alcohol Depend* **88**:259–71.

May PA, Gossage JP, Marais AS *et al*. (2008) Maternal risk factors for fetal alcohol syndrome and partial fetal alcohol syndrome in South Africa: a third study. *Alcohol Clin Exp Res* **32**:738–53.

Meschke LL, Holl JA, Messelt S. (2003) Assessing the risk of fetal alcohol syndrome: understanding substance use among pregnant women. *Neurotoxicol Teratol* **25**:667–74.

Morojele NK, Kachieng'a MA, Mokoko E *et al*. (2006) Alcohol use and sexual behaviour among risky drinkers and bar and shebeen patrons in Gauteng province, South Africa. *Soc Sci Med* **62**:217–27.

Morojele NK, London L, Olorunju SA *et al*. (2010) Predictors of risk of alcohol-exposed pregnancies among women in an urban and a rural area of South Africa. *Soc Sci Med* **70**:534–42.

Moyer A, Finney JW, Swearingen CE *et al*. (2002) Brief interventions for alcohol problems: a meta-analytic review of controlled investigations in treatment-seeking and non-treatment-seeking populations. *Addiction* **97**:279–92.

National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Department of Health and Human Services (2004) *Fetal Alcohol Syndrome: Guidelines for Referral and Diagnosis*. Available: http://www.cdc.gov/ncbddd/fasd/documents/fas_guidelines_accessible.pdf.

O'Connor MJ, Whaley SE. (2007) Brief intervention for alcohol use by pregnant women. *Am J Public Health* **97**:252–8.

Ojo OA, Louwagie G, Morojele N *et al*. (2010) Factors associated with female high-risk drinking in a rural and an urban South African site. *S Afr Med J* **100**:180–2.

Parker T, Maviglia MA, Lewis PT *et al*. (2010) Psychological distress among Plains Indian mothers with children referred to screening for fetal alcohol spectrum disorders. *Subst Abuse Treat Prev Policy* **5**:22.

Peltzer K, Ramlagan S. (2009) Alcohol use trends in South Africa. *J Social Sci* **18**:1–12.

Sobell LC, Agrawal S, Annis H *et al*. (2001) Cross-cultural evaluation of two drinking assessment instruments: alcohol timeline follow back and inventory of drinking situations. *Subst Use Misuse* **36**:313–31.

Stade BC, Bailey C, Dzendoletas D *et al*. (2009) Psychological and/or educational interventions for reducing alcohol consumption in pregnant women and women planning pregnancy. *Cochrane Database Syst Rev:* CD004228, 1–28.

Stratton K, Howe C, Battaglia FC (eds). (1996) *Fetal Alcohol Syndrome: Diagnosis, Epidemiology, Prevention, and Treatment*. Committee to Study Fetal Alcohol Syndrome, Institute of Medicine, Washington, DC, USA: National Academies Press.

Urban M, Chersich MF, Fourie LA *et al*. (2008) Fetal alcohol syndrome among grade 1 schoolchildren in Northern Cape Province: prevalence and risk factors. *S Afr Med J* **98**:877–82.

Viljoen DL, Craig P, Hymbaugh K *et al*. (2003) Fetal Alcohol Syndrome—South Africa. 2001. Morbidity and Mortality Weekly Report **52**: 660–2.

Viljoen DL, Gossage JP, Brooke L *et al*. (2005) Fetal alcohol syndrome epidemiology in a South African community: a second study of a very high prevalence area. J *Stud Alcohol* **66**:593–604.

Ward CL, Flisher AJ, Zissis C *et al*. (2003) Reliability of the beck depression inventory and the self-rating anxiety scale in a sample of South African adolescents. J Child *Adolesc Ment Health* **15**:73–5.

WHO (2001a) *Brief Intervention for Hazardous and Harmful Drinking. A Manual for Use in Primary Care*. Available: http://whqlibdoc.who.int/hq/2001/WHO_MSD_MSB_01.6b.pdf.

WHO (2001b) *AUDIT. The Alcohol Use Disorders Identification Test. Guidelines for Use in Primary Care*. Available: http://whqlibdoc.who.int/hq/2001/WHO_MSD_MSB_01.6a.pdf (16 May 2009, date last accessed).

WHO Anthro. *Child Growth Standards*. Available: http://www.who.int/childgrowth/software/en/.

CHAPTER 5: DISCUSSION

5.1 KEY FINDINGS

The thesis extends knowledge about FAS in South Africa. Studies 1-3 explore the prevalence of FAS in a diversity of environments and populations in the Northern and Western Cape provinces. This is supplemented by further data in study 4, and is supplemented by an assessment of the neurodevelopmental effects of prenatal alcohol exposure more generally (studies 6 and 7). The maternal factors associated with having a child with P/FAS are assessed in a range of settings, with a particular focus on changes in drinking practice during and after pregnancy (study 4). Lastly, an awareness-raising intervention is evaluated (study 5).

Studies 1-4 are the first to explore the prevalence of FAS in the Western and Northern Cape provinces outside of the Cape Winelands district. They demonstrate that the prevalence of FAS is high (near or above 50/1000) in all the communities studied in these provinces.

There was a rural-urban gradient, with higher prevalence in more isolated and rural communities. The prevalence of full FAS reached 10.0% in the isolated village of Aurora in the Western Cape (study 3), and the isolated town of de Aar in the Northern Cape (study 1). In all other communities, the rate of full FAS approximated 5% - this held not only for rural communities, but also for larger towns, as well as in the one city assessed.

FAS was not restricted to the SAC ethnic minority, and was found in the BSA population group which makes up 80% of the South African population, raising the possibility of FAS being a broader public health problem in South Africa. FAS was prevalent both in individuals of BSA ethnicity within predominantly SAC communities (study 1), and in at least one city with a predominantly BSA population (study 4). Overall, the findings suggested that prevalence in the SAC population group was quite high across all sites, whereas

in the BSA population it may be higher in more longstanding urbanised communities.

The study populations were characterised by predominantly low SES – this manifested for example with high rates of growth stunting in children: 11.9% were below the 5th centile in Kimberley (study 2), and 67% were <80% of expected weight in De Aar and Upington (study 1).

In a city with a level 2 hospital (i.e. with specialist staff), but where FAS had not been previously described as a frequent problem, none of 83 FAS cases had received a clinical diagnosis prior to the study, suggesting a great lack of awareness among health professionals.

The findings on prevalence of FAS should be linked to those of **study 7**, which explored the childhood neurodevelopmental trajectories of children with FAS to other prenatally alcohol-exposed children and to non-exposed controls. This study found a faltering developmental trajectory for all groups, shown in the GQ and especially the language domain. The FAS group were already lower functioning in infancy, and by 5 years the average GQ was in the borderline range. The PAE group were initially similar to the controls but by 5 years their average GQ was significantly lower. Differences between controls and the two alcohol exposed groups were particularly dramatic for the practical reasoning, performance and eye-hand domains. The findings reinforce the need to reduce risky alcohol use, and have implications for appropriate monitoring and interventions.

Study 4, taken together with findings of studies 1-3, confirms that irrespective of province, urban or rural residence, or ethnicity, drinking followed a similar drinking pattern: regular weekend binge drinking in groups together with partners, family or friends. Drinkers in the control group exhibited a similar but less regular binge-drinking pattern. The previously described association with the Dop system was rare.

There were some positive trends regarding drinking in pregnancy. Almost all drinkers in the control group stopped in the first or second trimester of pregnancy. A proportion of mothers to FAS children stopped through the course of pregnancy (varying from 21% to 54% across sites), more commonly at the site likely to be most exposed to

messaging on the risks of drinking in pregnancy. In addition, across all sites a majority (57%) of mothers to P/FAS children reported either stopping or at least reducing drinking during pregnancy.

Although women who stopped drinking tended to restart after pregnancy, with ongoing risk of another alcohol-exposed pregnancy, a significant finding was that cessation in pregnancy was associated with significantly higher odds of remaining abstinent at the time of interview (OR=3.3; 95%CI = 1.2-8.9).

Study 4 also highlighted a number of concerning findings. Few women perceived that they had a drinking problem, and a small proportion (7%) actually increased drinking in pregnancy. In the control group, twice as many women reported current drinking than just before the index pregnancy 7 years earlier. Women who stopped drinking in pregnancy usually resumed thereafter. At interview, 36% of mothers to a child with P/FAS (and 18% of controls) were not using contraception and were still drinking, and therefore potentially at risk of an AEP.

The maternal factors associated with FAS have mostly been previously described, but we identified some additional characteristics that are relevant to future prevention and treatment. A rather high proportion of mothers to children with P/FAS had died in the ~7 year interval from index pregnancy to interview: 13% across all study sites. This was often due to factors known to be potentially associated with alcohol use, such as tuberculosis and violence. Maternal mortality reached 29% at the Galeshewe in study 2. The exaggerated mortality at this site is likely related to the co-occurrence of alcohol use and HIV.

Partially as a result of maternal deaths, a relatively high proportion of children with FAS were in foster care (12%). Although a well-known association in developed countries, it has not been previously described in South Africa, and may be associated with improving access to social services.

Study 5 is the first published study on FASD prevention to use clinical endpoints. This before-after study investigated a multifaceted 'universal intervention', which included multiple media, as well as

CHW-driven health promotion activities, and education for health professionals.

The post-intervention prevalence of P/FAS was 5.7%, compared to 8.9% pre-intervention, a 30% decrease. Across the whole study population the median dysmorphology scores reduced significantly from 4 to 3, and since dysmorphisms are the features most closely associated with prenatal alcohol use, this may suggest that many women reduced drinking.

Interventions reached high coverage, with far more women in the post-intervention group reporting that they were aware of posters, and of radio or TV programs, and of information from nursing staff that addressed drinking in pregnancy. Post-intervention knowledge levels increased substantially, with over 90% being aware of the risk of a single drinking episode in pregnancy, compared to approximately 50% pre-intervention.

These findings suggest that a multifaceted CHW-driven 'universal intervention' may have significant effects, at least in populations with low prior knowledge of FAS. The findings support a more systematic approach to providing universal awareness-raising interventions.

5.2 DISCUSSION OF KEY FINDINGS

5.2.1 FAS prevalence

Overall prevalence

This thesis focused on FAS, since it is the most clearly defined diagnosis in the FASD spectrum [97]. Prevalence was determined using an active case ascertainment approach, which is perhaps the optimal approach to detecting prevalence of the condition within a defined geographical area, as summarised in section 1.6.2 of the literature review [165].

Studies 1-4 in this thesis describe prevalence of FAS, and partial FAS, among learners in a diversity of other environments in the Northern and Western Cape provinces of South Africa. Although one should be very wary of making directly comparisons across between different studies, in this case the methods were very similar and it seems reasonable to cautiously compare.

Taken together the studies provide information regarding the prevalence of FAS in learners in 67 schools across a time period spanning 2001 to 2013. The participants were all first grade learners, except at the single school in study 3 where all 171 learners were eligible. Across all sites, the study populations totalled 6048 learners, of which 83% were resident outside the Cape Winelands district, and 55% were resident in the Northern Cape.

The prevalence of FAS was very high at all study sites. Across all locations, a final diagnosis of FAS was made in 346 cases (57.2/1000), and of PFAS in 113 (18.7/1000), total P/FAS cases 459 (75.9 per 1000). The prevalence by geographical location is show in Table 7 and Figure 10 (the associated map) and ranged from 47.4 to 100.7 per 1000. The fact that FAS prevalence remained high across a 13 year period is consistent with the findings of Habbick et al.[199], who found that FAS prevalence did not diminish over time in a Canadian setting.

These prevalence rates can be compared to findings from studies performed internationally and in the Cape Winelands presented in

Table 5 (section 1.6.2 of the literature review). Outside of South Africa, the detected FAS prevalence rates range from 0.45 to 17 per 1000, which is 3 to 127 times lower than the aggregate prevalence found in the studies presented here.

Prevalence outside the Cape Winelands

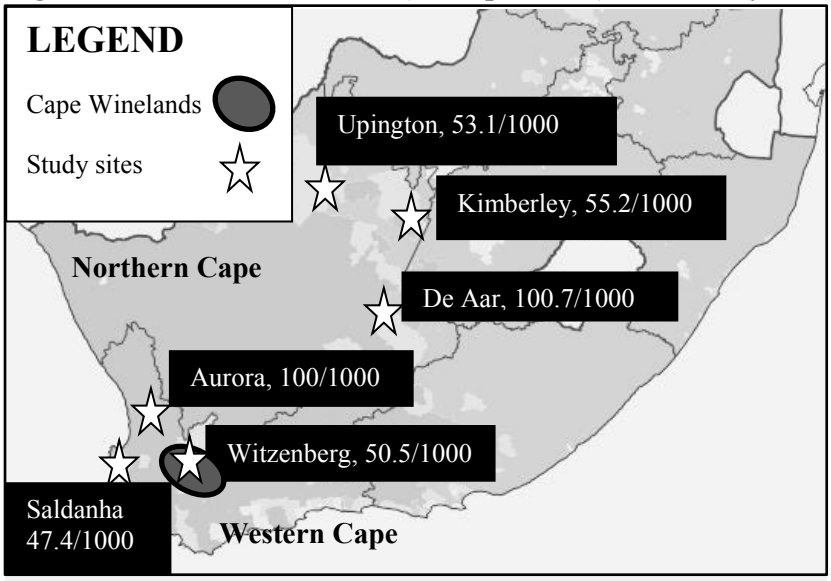
Comparing sites within and outside the Cape Winelands district, our studies found a prevalence of FAS of 50.5 per 1000 in the single site in the Cape Winelands district, compared to 58.6 per 1000 (295/5038) elsewhere. The prevalence of combined P/FAS in the Cape Winelands site was 87.1 per 1000, which appeared slightly higher than at the remaining sites (73.6 per 1000; 371/5038). In addition, compared to previous studies using similar methods in the Cape Winelands [139,140,167], our findings suggest that the prevalence rates at other sites are often just as high, and in some instances higher. This point is important since it eliminates the previously held possibility that the high prevalence in the Cape Winelands was an outlier as a result of the Dop system, which was known to be widely used in the area.

Table 7: Prevalence of FAS and PFAS per study site

Site (reference)	Site description	Sample size*	Cases (cases per 1000)		
			FAS	PFAS	Combined
De Aar 2001	Isolated town, Northern Cape	536	54 (100.7)	10 (18.7)	64 (119.4)
Upington 2002	Town, Northern Cape	1299	69 (53.1)	28 (21.6)	97 (74.7)
Witzenberg 2008	Towns/farms, Cape Winelands, Western Cape	1010	51 (50.5)	37 (36.6)	88 (87.1)
Aurora village 2011	Isolated village, Western Cape	160	16 (100.0)	6 (37.5)	22 (137.5)
Kimberley 2012	City, Northern Cape	1503	83 (55.2)	6 (4.0)	89 (59.2)
Saldanha Bay, 2013	Towns/villages Western cape	1540	73 (47.4)	26 (16.9)	99 (64.3)
TOTAL		6048	346 (57.2)	113 (18.6)	459 (75.9)

*Enrolled participants

Figure 10: Prevalence of FAS (cases per 1000) at all study sites



Ref: https://en.wikipedia.org/wiki/Demographics_of_South_Africa

Prevalence by province

Studies 1 and 2 provide all the extant information on prevalence of P/FAS among school-entry children in the Northern Cape, whereas studies 3 and 4 broaden the body of knowledge regarding prevalence of P/FAS in the Western Cape. The prevalence of full FAS was high in both provinces: 61.7 per 1000 (206/3338) learners in the Northern Cape, and 51.7 per 1000 (140/2710) in the Western Cape.

FAS is thus a considerable public health problem in several 'sentinel sites' within these two provinces. It may be argued that the surveillance sites are not representative of the provinces as a whole. To some extent this may be true, as requests for an area to be assessed were sometimes motivated by perceptions of a drinking problem in the area. Certainly all sites were predominantly of low SES, which is known to be a strong risk factor for FAS [192], and therefore include a limited representation of the smaller middle class populations which are likely to have lower prevalence rates.

More likely the study findings are generalisable to many similar areas of these provinces, for several reasons. The study sites represent a wide range of different settlements and populations. There are few specific differences between the study sites and neighbouring areas that would suggest that areas are unique. In addition, the findings are compatible with the evidence regarding drinking in the female population more generally, which is high in these provinces compared to most others, as described in section 1.3.2 of the literature review. The prevalence of FAS is in fact fairly similar to the prevalence of binge drinking in each province, and much lower than the overall prevalence of female drinking [44–47].

It is also noteworthy that the studies covered a considerable proportion of school entrants in the Northern Cape in particular, which increases confidence that the data may be representative of the situation in the province as a whole. The data pertain to three of the five districts in the Northern Cape, and each site represented a very different physical environment: a city with a mining history (the Galeshewe and Roodepan suburbs of Kimberley), a viticulture centre on the banks of the Gariep river (Upington), and a geographically isolated town (De Aar). Taken together, the populations of these four study sites comprise roughly 20% of the 1,150,000 population of the Northern Cape [242]. The two suburbs of Kimberley comprise over half the population of the city, and over 60% of grade one learners.

While there was less coverage of the Western Cape, the studies are the only existing evidence of FAS prevalence outside the Winelands district, and confirm high rates in two further areas.

Prevalence by place of residence

Both between studies and within studies we noted that smaller towns and more rural areas were associated with higher prevalence of FAS, in both the Western Cape and the Northern Cape. The prevalence of full FAS reached 10.0% in the isolated village of Aurora in the Western Cape (study 3), and in the isolated town of de Aar in the Northern Cape (study 1), considerably higher than at other study sites, where the prevalence of FAS approximated 5%.

In study 1 the prevalence of P/FAS in De Aar was 1.7-fold higher than in Upington. It seems reasonable to speculate that this relates at least in part to the different characteristics of the town, given the

existing evidence that neighbourhoods are known to have significant effects on drinking [202]. Compared to Upington, de Aar is a smaller and more isolated town with few recreation options and, until the very recent development of solar farms, very limited employment prospects.

A question arises as to whether the prevalence of FAS could relate to the Dop system. As discussed in section 1.9.2 (snapshot of historical alcohol use), the Dop system existed in the Cape Colony for centuries until the end of the Apartheid era in the early 1990s, although it now appears to be rare [48]. While the high prevalence of FAS in rural sites such as Aurora and Witzenberg could potentially be explained by relatively recent exposure to the Dop system, few women reported receiving Dop: one person (2%) currently received Dop in Kimberley (study 2), and 8 (5%) had previously received in Witzenberg (study 4).

In addition, the high FAS prevalence in urban areas is not consistent with a simplistic association between the Dop system and FAS. While the 'Dop system' was certainly an invidious historical component in entrenching risky drinking practices, it is now better conceived of as part of a broader web of factors, both old and new, associated with the high prevalence of FAS.

Another question is whether the high FAS prevalence in the Galeshewe suburb of Kimberley can be generalised to other townships in South Africa. This is important because urbanisation has accelerated since the demise of apartheid, which specifically limited it, and already over 60% of the population is urbanised [242]. Additionally, in the SA population as a whole female binge drinking is more prevalent in urban than rural areas [47]. Therefore, if Kimberley is representative of the situation in other townships, the scale of FAS could be very great indeed.

Currently only one other published study has directly appraised the prevalence of FAS in a South African city. This examined several small, non-representative samples of metropolitan Gauteng. It found similar FAS prevalence rates in predominantly SAC areas, but considerably lower rates in the predominantly BSA townships [168].

Prevalence by ethnic or population group

We also addressed the extent to which FAS as a public health concern is limited to the SAC population group. This arose because FAS in South Africa was initially detected in predominantly SAC populations [139,167], and female drinking is likewise heaviest in this population group [44–47].

As discussed in the literature review (sections 1.2.3 and 1.3.3) ethnicity and culture are associated with variation in drinking patterns [22,203], and in vulnerability to harm from a particular level of drinking [14,23]. Measured directly, FAS prevalence is higher in particular population groups [180,198].

It must be recognised that ethnicity is an imprecise term, and is a complex concept that encompasses ancestry, national group, birthplace and language - each of which could have distinct relationships to alcohol-related harm [261]. Despite the imprecision, there is increasing recognition that disparities between such groups are not reducible to social class differences, and warrant study [14,22,23]. A range of causes for such disparities have been proposed, including discrimination or perceptions thereof [211,262], neighbourhood factors [202], and cultural norms related to drinking [211].

We compared the SAC and BSA populations for two reasons. Firstly, the SAC is a putative high-risk group, whereas the BSA group is thought to be lower risk but it comprises the majority of South Africans. Secondly, these were the groups for which we had sufficient numbers to allow comparison.

In an urban area, study 2 compared suburbs previously designated for the SAC and BSA population groups (Roodepan and Galeshewe respectively), and whose ethnic composition still largely reflects this. The rate of P/FAS was somewhat, but not significantly, higher in Roodepan. In study 1 ethnicity data was available for the whole study population: no differences were noted in FAS prevalence for the study population as a whole, or for the larger Upington site, but in De Aar the prevalence was significantly higher among those reporting ethnicity as SAC. In study 4, cases at the Saldanha Bay site were significantly more likely to be SAC than community controls.

Overall the results were mixed, with some results suggesting higher prevalence in SAC individuals, but others showing no difference either related to reported ethnicity, or between communities which were previously designated along these lines. The most plausible explanation for the findings is that the BSA population is at lower risk in settings with a more traditional culture, for example newly established urban areas, where the population may be newly urbanised. More long-standing urban environments may be associated with breakdown of protective traditional mores through a process analogous to 'acculturation' [289](see section 1.7.3). Conversely, in the SAC population the long history of the Dop system would be expected to lead to high risk in rural environments, with subsequent urbanisation not changing this pattern much.

In summary, it would be prudent to recognise that individuals of SAC ancestry may have higher risk of FAS, but that it is by no means limited to this group. To the extent that FAS is increased among those of SAC, it is important to recognise its likely historical origins, and the risks of stereotyping. These two points can be briefly addressed by making reference to another minority population in which colonial history and stereotyping appear to play a role, namely the Native American population of North America.

In the Native American population, an extensive literature shows how 'historical trauma' related to a wide variety of aspects of colonial oppression and dispossession may impact on current social ills including hazardous alcohol use [263]. In parallel to this, it is likely that not only the Dop system, but a far broader range of historical factors including slavery, the near obliteration of the Khoisan people, dispossession of land, institutionalised racism and apartheid are in some way expressed in current risky drinking practices.

Stereotyping related to alcohol use is also well described, and Beauvais [204] states it thus: "Alcohol abuse and alcoholism have caused compounded problems for American Indian and Alaska Native peoples. In addition to the enormous physical and emotional tolls, the problems also have led to an unfortunate stereotype that has further burdened the Native communities of North America. This stereotype has perpetuated the image that all Indian people are afflicted with alcohol problems".

5.2.2 Lack of prior clinical detection of FAS cases

Family members or guardians are informed of the participants FAS status at a feedback visit. At this visit (study 2) the counsellor noted whether the clients had any prior knowledge of the diagnosis. None of the 83 cases of FAS were reported to have received a previous diagnosis, despite the fact that the study occurred over a decade after the initial demonstration that FAS was common in a South African population.

As mentioned in the literature review (section 1.5.6), under-identification of FAS is common [155,156]), even where the mother is known to be abusing alcohol - because this history is often not obtained [157]. If asked, South African women are usually forthcoming about their drinking [264], but the severe under-diagnosis of FAS suggests that history-taking regarding in-pregnancy drinking make be inadequate or disregarded, and also that health professionals lack the skills to make a clinical diagnosis of FAS.

In South Africa FAS clearly remains severely under-diagnosed despite the fact that it has received considerable media attention, at least in parts of the country where FAS has not been identified as a common problem. Lack of diagnosis denies an opportunity for early developmental intervention in the affected child [123]. In addition, the mother of a P/FAS child is at high risk of having other affected children [265], a risk that Autti-Rämö *et al* [266] found to be 43%. Lack of diagnosis therefore also profoundly affects the risk of having further affected family members.

5.2.3 FAS and neurodevelopment

It is instructive to link the findings of the FAS prevalence surveys to **study 6 and 7** (annexures 1 and 2 respectively), which present longitudinal data on neurodevelopmental outcomes from infancy until 5 years of age for a subset of children from the De Aar site of study 5. This contrasts with other published South African studies of neurodevelopment, which have been cross-sectional in design [109,118,264,267].

In study 7 neurodevelopmental outcomes at 5 years of age were assessed for three study groups: (1) FAS (2) Prenatal alcohol exposure but non-syndromic (PAE) (3) Unexposed controls. Importantly, even the mothers of the PAE group tended not to be light drinkers, and took a mean of 13 standard drinks per week, usually in a predominantly weekend binge drinking pattern.

The study found a faltering developmental trajectory for all groups, shown in the GQ and especially the language domain. This is consistent with the strong evidence that child development is compromised by poverty related factors, both biological such as poor prenatal or postnatal nutrition, and psychosocial such as poor parenting skills and under-stimulation, or exposure to violence [117,268].

It is also consistent with a cross-sectional study of school entrants in a community with a high FAS prevalence in the Cape Winelands [152], which attempted to assess the prevalence of the full spectrum of adverse development effects in PAE children. The study estimated that 13.6%-20.9% had FASD, with up to a quarter of cases being ARND (i.e. non-syndromic). Despite this, when all children were assessed for factors associated with poor neurodevelopmental status, there was a bigger effect from broader factors associated with low SES than from prenatal alcohol exposure [118,264].

The FAS group were already lower functioning in infancy, and by 5 years had GQs in the borderline range, whereas the PAE group were initially similar to the controls but by 5 years their average GQ was significantly lower. Differences between controls and the two alcohol exposed groups were particularly dramatic for the domains of practical reasoning, performance and eye-hand coordination. This is consistent with the extensive literature showing that the

developmental deficits in FASD relate to higher cognitive functions across a range of domains [101,107,108,267].

The drop-off in the PAE group could therefore be explained by prenatal effects on more advanced brain functions, or the effects of alcohol on parenting or other post-natal circumstances, or very likely a combination of these. In either case the findings confirm that, even in the most vulnerable women, with risky drinking patterns and living in low income developing country environments, FAS is only subset of the adverse neurodevelopmental outcomes of PAE.

The findings suggest that the approach to early child development should support parenting and early learning in all children, have an additional focus on PAE children, and aim for early diagnosis of FAS.

On multivariate analysis, earlier recognition of pregnancy was linked with better developmental functioning at year 5, especially amongst the FAS group. The most likely explanation for this is that improved child development results from cessation or reduction of drinking in pregnancy. This reinforces the need to increase awareness of the risks of prenatal alcohol exposure, to encourage early initiation of antenatal care and to screen for alcohol use and provide appropriate interventions.

5.2.4 Drinking practices and changes in drinking during pregnancy

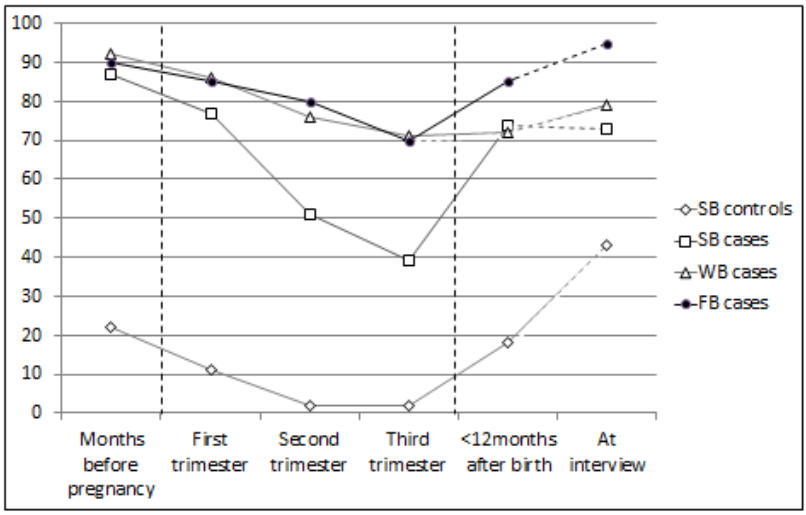
Across all studies, the vast majority of mothers to children with P/FAS disclosed the expected pattern of regular weekend binge drinking during or shortly before the index pregnancy. In some instances proxy informants were unaware whether the mother had taking alcohol, and in a small minority mothers denied drinking (in some instances the interviewer questioned the veracity of this information).

Study 4 explored interview information regarding change of drinking practice over time. Over 90% of control women reported cessation in pregnancy, compared to half of cases at the same site, and under a third at the two earlier sites – this is demonstrated graphically in Figure 11 (reproduced from study 4). Rates of cessation of drinking among control women are consistent with similar reductions of binge

drinking during pregnancy found in population-based studies in the USA [55,56] and more dramatic than found studies in other populations with known high rates of binge drinking - for example studies of Russian women [269] and Inuit women [62].

It is likely that inter-site variations in cessation of drinking relate to different levels of awareness of the risks of drinking in pregnancy. The site with greatest reduction in drinking had several features suggesting higher awareness: it is the most recently studied site, predominantly urban, and located in the Western Cape, which is the province with the most active alcohol awareness programs. The fact that the surveys show increasing rates of cessation in the chronological order performed is also consistent with growing awareness. A similar temporal trend is visible (but has not been remarked upon) on inspection of a separate series of FAS prevalence surveys in a single site the Cape Winelands [139,140,152,167].

Figure 11: Percentage of women drinking per site before, during and after pregnancy



Unfortunately, reduction of drinking was often 'too little, too late' to prevent FAS, in part probably because of delayed pregnancy

recognition, which occurred at a median 3 months gestation among both cases and controls, compared 6 weeks in North American women [270] . Given that the first trimester is the critical period for development of FAS [76] there is a particular need to encourage early initiation of antenatal care with the aim to reduce risky drinking and use of other substances and teratogens.

There have been reports in the lay press in South Africa that women deliberately increase drinking in pregnancy to give their child FAS and thereby become eligible for a disability grant [271]. This idea mirrors similar local claims that women deliberately become pregnant to secure access to the child support grant, or seek infection with HIV in order to qualify for a disability grant [272], despite scant supportive evidence [273]. Study 4 shows that across all sites only a small minority of women (8/121, 7%) increased drinking.

Although increased drinking in pregnancy is relatively uncommon in our studies, it is important to consider the possible causes. Watt *et al* [274], in a qualitative study of women attending taverns in Cape Town, reported four main factors associated with ongoing or increased drinking in pregnancy: stress including that related to pregnancy, peer group norms supporting drinking and drinking to retain social connection during a period of life transition, lack of attachment to the pregnancy or resistance to motherhood, and physiological addiction. Participants' free-text comments in study 4 supported stress as a cause: of eight women increasing drinking, five reported being 'very' or 'extremely' stressed. All were farm labourers, which may also be relevant because pregnant female farm workers are a particularly vulnerable and disempowered group [240].

Study 4 also demonstrates that women tended to restart drinking fairly soon after the index pregnancy. This is not dissimilar to findings in the USA, where most women stop drinking in pregnancy but many restart within months thereafter [57]. However, it has not previously been described in a South African context, or in very high risk drinkers such as mothers of children with FAS. Importantly, a history of cessation in pregnancy was associated with less likelihood of drinking at the time of interview over 7 years later, and may therefore be associated with reduced drinking in the longer term.

Although this gives some cause for hope, there were also less encouraging signs. At interview, 36% of case women (similar between sites) and 18% of controls remained at potential risk of an AEP because they were still drinking but not using any form of contraception. Almost half of women were not using contraception, with no difference between cases and controls, and the large majority of index pregnancies were unplanned. It is known that southern Africa has an unusually high prevalence of unintended pregnancy - 59% compared to the international average of 41% [275] - but among case mothers from study 4, the proportion was as high as 75%. Using pooled data from studies 1, 2 and 4, the trend was similar: 67% (78/117) of control mothers and 77% (202/263) of case mothers reported that the index pregnancy was unintended.

An additional concern was that, despite the high prevalence of drinking - often in a binge-drinking pattern - only 6% of cases perceived that they had a current problem with drinking. A larger proportion (14%) of case women would contemplate an intervention for drinking, although only 1 (0.7%) had received treatment to date. An apparently contradictory finding was that over 80% of case mothers had tried to stop drinking in the past. It was unclear whether this related primarily to the reported reductions in pregnancy, or whether women had made other efforts to stop drinking.

Taken together, these findings show there is scope for interventions to reduce drinking, in that even high-risk women appear to be increasingly inclined to stop drinking in pregnancy, and this is associated with less likelihood of drinking in the long-term. The fact that pregnancy is also the one time when local health providers are most likely to ask about drinking, suggests that this is priority time at which to implement selective interventions. It is important to reinforce the message in the pueperium to minimise recommencement of drinking.

There are a number of further factors to consider. Most high-risk drinkers are unaware of, or perhaps in denial about, the nature of their drinking. Despite this, the twenty-fold difference in the proportions of women interested in treatment and those who had received it, indicates a considerable unmet need for brief intervention and treatment services. The rather low use of contraceptives and very high proportion of unplanned pregnancies stresses the need for more

effective and contraceptive services and family planning messages. This has recently been prioritised by the South African Department of Health. Lastly, late recognition of pregnancy undermines attempts to reduce ongoing drinking, and also needs to be addressed.

5.2.5 Risk factors for FAS

Demographic and anthropometric risk factors

As discussed in the literature review (section 1.7.3), there is much quantitative information available on risk factors for FAS, both internationally [149,187,192,196,276,277] and relating to the predominantly SAC population of the Cape Winelands [138,140,152,158,167,278]. May and Gossage [180] give a rather detailed account of risk factors in South African, Italian and American cohorts. They and other authors have noted the very wide range of risk factors that have been described, including maternal age, other demographic features, maternal anthropometry, reproductive factors, and smoking or other drug use, but have also noted that many of these are associated with low SES [192,279]. It has been further suggested that, although FASD and alcohol-related harms more generally are commoner in those of low SES, within this group they are commoner in further marginalised groups such as racial/ethnic minorities [16,22].

Studies 1, 2 and 4 assessed a range of risk factors in various South African environments using different approaches. Study 1 compared mothers of cases and controls matched for age, sex and ethnicity; study 2 compared case mothers from two different suburbs catering to women of different population groups; study 4 compare case mothers of SAC ethnicity across 3 different sites to each other and to community controls at one site.

Broadly speaking, the studies concurred that, irrespective of site or ethnicity, most case mothers shared a background of low family income, high unemployment rates, relatively low educational levels, and other features in keeping with low SES. Study 4 detected a variety of differences between SAC case women at different sites, but these were often expected based on the nature of the site. For example, women in at a more rural site had higher employment rates but lower levels of education than elsewhere. This was expected

because many were farm labourers, and the farm-work sector is known to have particularly high rates of functional illiteracy [238].

It was expected that smoking in pregnancy would be more common in cases than controls, but we also found considerable inter-site variation. It is possible that public health measures to reduce smoking (e.g. increased pricing) are having an effect, as smoking prevalence was lower in the later studies. The infrequent use of other drugs probably reflects the fact that alcohol use in these settings has not been historically linked to use of other drugs, though this pattern is changing in metropolitan areas [280].

More advanced maternal age at the time of pregnancy is a well-described risk factor for FAS [180], though it has not been consistently found in our or other studies of predominantly SAC populations in SA [138]. A striking finding in study 2 was that women in Galeshewe were considerably older than Roodepan women, which suggests that risk for FAS may evolve more slowly in this predominantly BSA group. This may relate to differences in drinking patterns, or indicate the possibility of a differential 'weathering' effect, as mentioned in section 1.7.3.

There is a known association between FAS and low maternal BMI [180]. In study 4, maternal anthropometry varied considerably between study groups. Control women had an average BMI in the obese range, consistent with increasing and currently high rates of obesity in South African females [281], especially in the poor, urban female demographic [282]. As expected, case mothers were of smaller body habitus, but with significant inter-site variation, with over 40% of SAC case women in Kimberley having a BMI in the underweight range. This places them at increased risk of having a child with FAS, as well as other poor pregnancy outcomes [283].

Social factors associated with FAS

In study 4 case children were more likely to have received placement in foster care or spent prolonged periods with relatives. The latter is, in part, a reflection of the tendency in many South African settings for relatives to take on child-rearing roles [284]. However, placement in formal foster care, was a strong marker for FAS at all sites: 12% of

children with FAS were in foster care, and odds of being in foster care were over 7-fold higher than in the control group.

Although foster care populations are known to have higher prevalence of FAS in societies with well-developed social services [209,270,285,286], this has not previously been shown in South Africa. It is , however, recognised that parents with alcohol use disorders are likely candidates for requiring foster placement in view of the effects of the associate chaotic lifestyle, likely exacerbated by other effects of poverty, which itself "can significantly undermine parenting" [287]. Social services have been prioritised in recent years and it is likely that the availability of foster care to children in high risk populations has improved. There is an associated need for FAS surveillance for children in foster or institutional care.

An important reason for children being in the care of others was maternal death. This issue was addressed in studies 2, 3 and 4. In a total of 294 cases of P/FAS there were 39 (13%) maternal deaths occurring in the approximately 7 years between the index pregnancy and the time of interview. Galeshewe, the mainly BSA community in Kimberley, was an outlier with a 29% maternal mortality rate, significantly higher than in Roodepan (the comparison community in Kimberley).

We did not collect information regarding cause of maternal death, but as discussed in section 1.2.2 binge drinking has many health risks, including unintentional injury, interpersonal violence, and unsafe sex [6,288,289]. Unsafe sex in turn increases risk for contracting HIV, and binge drinking specifically has been demonstrated to increase the risk of contracting HIV [51] and of poor HIV treatment outcomes [290].

The extremely high maternal mortality rate in mothers of FAS cases in Galeshewe is likely to relate to the conjunction of alcohol use and HIV infection, which is the commonest cause of death in adults in the Northern Cape [291], and is twice as common in Galeshewe as in the comparison community Roodepan (Northern Cape province Department of Health, unpublished data), while there is no evidence that other possible causes, such as violence and injury, differ substantially between the two communities.

5.2.6 Preventive interventions

Study 5 is a before-after study of a multi-faceted, community-level intervention. It was conducted in a population that was previously documented to be at very high-risk for FAS in study 1. The intervention represented the first substantial FASD-prevention intervention in these communities, and it was therefore anticipated that the community would have limited prior knowledge of the risk of FAS.

The intervention was driven by community members employed as CHWs, and pamphlets and posters were developed together with community members. This attempted to ensure that the intervention was responsive to the needs of the community, and was culturally appropriate to the community, a feature which is important to the success of such intervention [201].

Important findings in the entire study group were a reduced rate of P/FAS, and a reduced dysmorphology score in the entire post-intervention cohort compared to pre-intervention. By comparison however, no change was detected in neurodevelopmental outcome (in the subset of cases and controls), and the anthropometric findings were mixed.

The decreased dysmorphology score in the whole study population post-intervention, and the decrease in proportion of cases diagnosed with P/FAS (which requires syndromic features) are mutually consistent. Unlike other adverse outcomes of prenatal alcohol use, the dysmorphic effects are specific to early pregnancy. As mentioned in section 1.5.2 , May *et al* [180,197] showed that the dysmorphic effects are the outcomes most strongly correlated with prenatal alcohol use, and that there is a high correlation between total dysmorphology score and prenatal alcohol use. The finding of a decreased dysmorphology score post-intervention may therefore suggest a reduction not only of the prevalence of P/FAS, but of alcohol consumption by a broad range of drinkers.

The fact that no effect was found on neurodevelopment was unfortunate. However, for practical reasons the neurodevelopmental assessments were done relatively early in life, meaning that less severe effects would not be detectable, as was demonstrated in the

subset followed up to 5 years (study 7). In addition, neurodevelopment is subject to a much wider range of prenatal and postnatal influences than dysmorphic features, and the alcohol-related component is therefore more difficult to detect (May et al, 2013).

In the subset of mothers who were interviewed, there was a considerable increase post-intervention in knowledge, and increased perception of the persuasive value of awareness-raising in changing women's drinking practices during pregnancy. A higher proportion of interviewees recalled receiving information related to FASD at clinics and on the radio or television. While it is well accepted that knowledge alone does not produce behaviour change, it is an essential first step, and the improvements in knowledge are consistent with the changes in FAS prevalence and dysmorphology scores.

Pre-intervention, only half of women were aware of the risk of FAS associated with alcohol use in pregnancy, and there was little awareness of the difference in risk between light drinking and binge drinking. The dramatic 5.8-10.3 fold improvement in odds of correct knowledge post-intervention is likely to in part reflect poor prior knowledge. This would be consistent with findings in other studies of awareness-raising interventions, among African-American women, where those with less prior knowledge showed greater improvement with the intervention [215,216].

The intervention provided was multi-faceted and quite intensive. It included pamphlets, posters, health talks at clinics and other community venues, and drama productions. It is not possible to comment on the most effective component. However, the fact that this multi-component intervention was successful is consistent with the finding of Kaskutas and Graves [212] in the USA population that women reporting exposure to more types of media were more likely to reduce alcohol consumption in pregnancy.

In a survey conducted at a similar time to study 5, but in the Cape Winelands, Parry *et al* [292] found baseline knowledge of potential harms from alcohol consumption to be significantly better than was found in the pre-intervention arm of study 5, but somewhat less good than post-intervention. This better baseline knowledge is unsurprising, as the Cape Winelands have been a focus for FAS-related activities since the 1990s. The authors raised concerns about

the fact that, similar to the pre-intervention arm of study 5, over 30% of women had not heard health talks about FAS, and they stressed the need for awareness-raising.

It is important to ensure that education, awareness and persuasion approaches receive due consideration in a South African context. Policy changes such as a ban on alcohol advertising are seen as the most cost effective manner in which to reduce alcohol consumption [15,293], and there been a strong push for a ban on advertising alcohol in South Africa [294], with resistance from the liquor industry leading to a stalemate [295]. Perhaps as a result, other approaches to prevention have been inadequately assessed.

The educational approach has received little attention in part because it is considered less cost-effective than policy change [15], but perhaps also because it is cast as the approach that the alcohol industry supports [232,294]. A similar concern has been expressed about targeting FAS and prenatal alcohol use, rather than using more general policy approaches [232].

These concerns are relevant, although the approaches need not be mutually exclusive. In addition, Schmidt *et al* (2010) identified a need for interventions that target the poor, because of the association between low SES and increased alcohol-related harm. In the context of the educational deprivation that was consciously engineered under apartheid, and that remains present (as evidenced by the very poor academic performance of South African school learners compared to their peers internationally), it can be argued that health promotion targeted at low SES communities is both empowering them with knowledge, and targeting those at highest risk.

In addition, given that many even high-risk women consider stopping drinking in pregnancy (study 4), it seems pragmatic to target drinking in pregnancy, though with the intention of also addressing the other harms of alcohol, and impacting on the drinking practices of others such as friends and family members.

Since study 5 assesses a predominantly CHW-driven intervention, it is of interest that South Africa is currently developing a health promotion program to be delivered by CHWs, primarily aimed at HIV prevention and treatment. However, HIV infections occur in a broader

context, and people living with HIV and AIDS have high rates of risky drinking (Brittain et al. 2017), and both HIV and risky drinking have similar associations with psychosocial factors such as depression and intimate partner violence [296]. Rotheram-Borus *et al* [219] found that a CHW-driven intervention focusing on health promotion and behaviour change related to alcohol use, partner violence and depression was associated with improved measures of mental health, and reduced alcohol use in pregnancy. Our findings support their recommendation that the role of CHWs not be limited to HIV, and that they be trained to take on a broader behaviour change role.

5.3 LIMITATIONS

5.3.1 Prevalence surveys

The complexities of diagnosing FAS hamper efforts to quantify its burden of disease and institute ongoing FAS surveillance - for example, the diagnosis requires a multistep clinical process and, and several classification systems are used, with somewhat different diagnostic criteria [97,148]. However, strengths of the surveys were that the clinical team always comprised members with appropriate expertise, and the classification system used is widely accepted and was developed in part using South African populations.

Ideally FAS cases should be compared to a control group to ensure that findings are not simply reflective of the general population. Due to capacity and funding constraints, control groups could not be used in all studies. However, the studies where control groups were available (study 1 and study 4) yielded the expected differences between cases and controls.

Individual surveys varied in their response rates, often due to local factors. In study 1 the interview response rate was somewhat suboptimal at 77%. This related to the fact that the study was chronologically the first and retention methods were still being optimised, but it was also because the site was remote and a key interviewer died during the course of the study. In contrast, complete

ascertainment of FAS status was achieved in 95% of participants in study 2. It should be noted that retention is usually more difficult for women with a drinking problem, and therefore a lower retention rate is likely to reduce rather than increase the estimate of FAS prevalence. Also of note is that published surveys conducted outside South Africa often have much lower participation than in any of our studies, for example a 25% consent rate was described by Clarren *et al* (2001)[156].

The neurodevelopmental assessment tools used varied between study 1 and the remaining prevalence surveys, but in both cases were well accepted in South Africa and elsewhere. In studies where controls were available for comparison, significant differences were found between the P/FAS and controls in the expected domains. Given that the populations studied were not homogeneous, caution is required in comparing results from children of diverse backgrounds, for example due to cultural differences, or related to the use of interpreters in some cases but not others. We therefore did not comment on such differences found in study 7.

Further limitations stem from use of the GMDS-ER tool used in most studies, which tends to measure general ability, but is less able to detect subtle or specific delays [109]. As previously noted (section 3.4.1), direct comparisons between domains in the GMDS-ER are prone to misinterpretation due to differing means and standard deviations of the sub-scales [243].

The fact that neurodevelopmental assessments were performed only on children clinically suspected of FAS results in under-assessment of the full spectrum of FASD. It is an unavoidable deficiency of the survey method, which focuses on identification of FAS. This was partially ameliorated by the studies of longitudinal neurodevelopment which described the nature of neurodevelopmental problems in non-syndromic cases although they did not accurately assess the prevalence of such cases.

Prevalence rates were quoted for all grade one learners and may be inflated if learners with FASD more often repeat the grade than others. A post-hoc correction was made for this in studies 1 and 2, and resulted in an 8-24% reduction in estimated prevalence, although prevalence remained high in all areas.

Generalising our findings to other geographical areas is uncertain in view of the possibility of systematic differences between the populations studied and those of other rural or urban areas. However, the high prevalence of FAS across a wide range of study sites with very varied characteristics increases confidence that the findings are representative of the situation in much of the Western and Northern Cape provinces, though not necessarily other parts of South Africa.

As mentioned previously, study 2 raises question about the extent to which the high prevalence of FAS in Galeshewe is generalizable to townships elsewhere in South Africa. This is unclear, because it is uncertain whether it relates to features that Galeshewe shares with other townships, or that are unique.

If broad socio-economic factors such as unemployment and poverty are important, then Galeshewe has features in common with many other townships in South Africa. However, there may be more specific historical factors at play. In this respect, Galeshewe is atypical since Kimberley and Galeshewe are amongst the oldest urban settlements in the interior of South Africa.

The record indicates a long history of problem drinking in Kimberley, with 'drinking, fighting, beer making and gambling' already frequent in the early twentieth century (unpublished data, Lunderstedt, 2000). In addition, there is evidence to suggest a history of female drinking: the municipal beer halls established in the 1940s had separate drinking areas for women (unpublished data, Allen et al, 2004). As mentioned, the long history of Galeshewe may have allowed for attrition of socio-cultural prohibitions on female drinking among BSA women, similar to descriptions of 'acculturation' in other populations [297,298]. Another factor that may be specific to Kimberley is the economic decline in recent decades due to downscaling of mining activity. This may be relevant, since there is good evidence that binge drinking increases during economic downturns – amongst both unemployed and employed individuals [299].

In most instances we have not been able to do follow-up studies in the same areas where the initial surveys were done due to resource limitations. This is important because there is some evidence that the prevalence of FAS is increasing [139,140,152,167]. One partial exception to this is in De Aar / Upington where the data from article 1 and the pre-intervention arm in article 5 can be compared. These assessed

children born in 1994-7 and 2002-5 respectively, though at different postnatal ages. Of interest is that P/FAS rates were similar. In De Aar the school survey found a P/FAS rate of 10.1-11.9% (depending on whether or not children who may have been repeating the grade were included) compared to 11.3% in the pre-intervention arm. In Upington the corresponding figures were 4.9-7.5% versus 6.6%. Given the different ages of the participants and different neurodevelopmental assessment techniques applied, the comparison of studies 1 and 5 should be interpreted with caution.

5.3.2 Cross-site questionnaire

The methods used for the surveys were similar between sites. However, they were conducted at different times, so it is not possible to be sure whether differences detected between sites are due to differences between sites or changes over time. In view of some changes in the questionnaire over time, and the fact that we chose to analyse only data that was available for all sites, some questions were excluded. However a wide range of alcohol-related and other variables could be assessed. A control group was only available for one site, but nevertheless provided an important point of comparison.

A small proportion of interviewees were considered by the interviewers to be unreliable. In addition, the proportion of case women who denied using alcohol in pregnancy (10%) was somewhat higher than in previous South African studies [140]. It is possible that a small minority of cases were misclassified as P/FAS, or alternatively that the responses indicate social desirability bias or recall bias. Since drinking in pregnancy is potentially stigmatised, studies that rely on self-reported drinking behaviour are prone to social desirability bias. As discussed in section 1.5.4, retrospective studies are also subject to recall bias, and also recall may be directly affected by binge drinking, or by the 7-8 year interval between the index pregnancy and the interview. Despite these potential problems, there is evidence that retrospective methods are relatively accurate compared to obtaining a history during pregnancy [142].

Because most available interview data pertained to women in the mixed ancestry SAC minority group, and because ethnicity is a determinant of drink-related harm [23], we decided to restrict our focus

to this group. However, the study did cover a wide range of environments. Therefore the data are likely to be representative of many mothers of FAS children in the SAC population group, but caution is necessary when generalising beyond this group.

5.3.3 Prevention study

The before-after study design, and the lack of a control group, means that the design is relatively weak. A more robust experimental design was deemed unfeasible given the limited study resources available. The intervention was provided at community level which would then have required a set of clusters, or a stepped wedge design, for example, beyond the available resources. The rather weak design limits the ability to draw firm inferences, and the assessment of the intervention cannot be considered definitive. It is difficult to attribute the reduction in P/FAS to the intervention alone, as concurrent changes in the community might account for at least part of these effects. However, the lack of change in tobacco use and employment status, suggest that temporal changes do not account for all the effects noted in this study. National programs for reducing drinking were, and remain, weakly developed in South Africa and are unlikely to have interfered with our intervention.

The biggest strength of the study is the use of clinical outcome data, such as P/FAS and population level dysmorphology scores rather than relying only on proxy data such as self-reported alcohol use, as in previous studies. Addition strengths include the relatively large study population, the fact that all births during a defined period were eligible for inclusion, and the fact that the same clinical team performed the clinical assessments before and after the intervention.

The study had some other weaknesses. Collecting information only on mothers of cases and controls, as opposed to all women, reduced the ability or power to detect differences between women's behaviour in phase one and phase three, though differences in maternal knowledge of alcohol risks were very distinct. The absence of data on the participation rates for two of the four cohorts should be noted, as this information is important for judging the likelihood of selection bias. Data were also missing for some other study variables, mostly due to incomplete information in the multiple data sources used.

The study therefore provides supportive evidence for a CHW-driven health promotion intervention to increase awareness of the risk of drinking in pregnancy and reduce P/FAS, in the context of town populations with low prior knowledge of the risks of drinking in pregnancy. Although low prior knowledge has been the rule in South Africa[300], the intervention effect may be less evident in populations with higher prior knowledge [216]. The intervention may also be less effective in larger or more transient populations. Because the intervention was broad and multifaceted, it is not possible to specify which components were most effective although information was gathered on which sources of information mothers remembered best.

CHAPTER 6: RECOMMENDATIONS

6.1 RECOMMENDATIONS FOR POLICIES

The data provided in these, and other referenced studies give sufficient evidence that FAS and FASD are serious public health problems within and throughout the Western and Northern Cape provinces of South Africa.

In contrast, the policy response has been minimal, aside from a few broad measures such as increased taxation on alcohol. A particular problem has been the lack of policy at sector level, for example within the health sector. It is beyond the scope of this discussion to address the reasons for this, but sector level policies need to been developed. The studies presented in this thesis speak to a range of possible interventions, predominantly within health services, and these will be briefly discussed. Given the limited nature of existing services, and the wide range of policy changes required, some of the recommendations are stated quite broadly, and assume a need for further disaggregation.

Within the health service there is a need to formulate workable policy recommendations regarding monitoring, diagnosis, treatment and prevention. These should take into account the existing knowledge about why women continue to drink in pregnancy, and what interventions work. The methodological detail for developing effective theory-based interventions has been discussed by other authors – for example Roozen *et al* [301] describe an intervention-mapping approach to promoting drink-reduction in pregnancy.

Monitoring and surveillance: Complementary to monitoring for FAS (which is perhaps best considered a research activity, rather than a surveillance one, due to the complex multistep process involved), there is a need for appropriate surveillance of drinking. There is an especial need to monitor binge-drinking, and in females especially

related to pregnancy. A review of the National Health Indicators is advisable to determine whether they adequately capture alcohol-related information – it would be important to include a question on binge-drinking in the previous 3 months. Current monitoring systems appear to fall short: the most recent version of the annual South African Health Review [302] contains minimal reference to alcohol and only passing reference to FAS, and the District Health Barometer publishes no alcohol related metrics [303].

Universal interventions: An awareness-raising intervention (study 5) showed a large effect on maternal knowledge of drinking risks among expectant women, at least in a situation where prior knowledge was low.

- At a minimum this indicates the value of a multiple media approach in antenatal clinics. Several of the following should be applied: health talks, videos, posters and social media messaging, and these provide a clear and accessible message.
- Study 5 also gave supportive evidence that CHW-driven health promotion regarding risky drinking in pregnancy is effective. National CHW-based health promotion should include targeting of alcohol-related behaviour change.
- Consideration of alcohol use needs to be included in broader interventions targeting pregnant women. Chersich *et al* [304] recommend the provision of a cash grant to pregnant women, based on compelling evidence that pregnancy support programs in developing countries have been shown to improve both maternal and fetal outcomes, and are predominantly spent on food with no current evidence that they increase alcohol use. Should such a grant be introduced, there is a need to include concurrent messaging regarding the risks of alcohol use in pregnancy and to monitor alcohol use.

Selective intervention in pregnancy: Sufficient international and local data exist to show the efficacy of screening, brief interventions and referral to treatment (SBIRT) type interventions (section 1.8). However, no system currently exists to provide SBIRT in South Africa. A number of policy recommendations are appropriate and study 4 speaks to several of these.

- Information given to the public, and to reproductive age or pregnant women, must give the unambiguous recommendation that women should not drink any alcohol in pregnancy (Surgeon General of the United States of America 2005). Mixed messages can lead to confusion both among professionals and the public, especially in an environment where knowledge is relatively limited (study 5).
- Study 4 indicates that even high-risk drinkers consider stopping or reducing drinking in pregnancy. In addition, the first antenatal visit is the one time when women are routinely asked about alcohol consumption. There is a need for this to be optimised as an opportunity, but the current approach is not systematic, and women are simply asked whether they drink or not. The evidence indicates that screening for alcohol use is best performed with a tool validated for use in pregnant women such as the AUDIT, TWEAK or T-ACE tests.
- If alcohol use is disclosed there is presently also no pre-set approach to handling this information, and it is currently unclear whether or how staff respond. There is a need for staff to stratify risk appropriately and provide a brief motivational intervention if required. This needs to be tailored to the skills and time constraints of the staff, and only a few minutes may be possible.
- A history of risky drinking tends not to be followed up after the first antenatal visit (Waterman et al, 2013). It is important that the message be reinforced, even if briefly, and the follow-up antenatal visits provide an ideal scaffold for this [305].
- Women who stop drinking in pregnancy tend to restart fairly soon thereafter (study 4). The issue of risky drinking should be revisited at this time. Discussion should include the option of abstinence from alcohol, but emphasise the risk associated with binge drinking. It is best linked to a discussion of contraception and family planning, and the concept should be promoted among women that if they do any risky drinking they should be using contraception and family planning.
- The risk of peri-conceptional drinking is aggravated by late recognition of pregnancy (study 4). The need to address in-pregnancy drinking, and other substance use, should be

highlighted as a key reason for early initiation of antenatal care.

- Particular attention should be paid to women with risk factors for AEP and FAS. These include older women and those who use other substances. Smoking is a common cofactor, and preventive messaging should be addressed along with alcohol.
- Referral options, such as a 12-step program or drug-rehabilitation centre is available in many settings. Better awareness of these is required in healthcare settings.
- The optimal situation is complete prevention of AEPs through planned pregnancies. This requires an approach which is not limited to pregnancy. At a minimum, opportunistic screening for alcohol use should be encouraged at all healthcare visits. In this regard, family planning clinics are an obvious target as they deal specifically with reproductive age, non-pregnant women.

Nutritional interventions: Mothers of FAS children are on average of significantly smaller body habitus than controls, and especially so at some sites. Although women who are underweight or who give a history of binge-drinking may be at particular risk of nutritional deficiencies, interventions may be best targeted at all women of limited means. Possible interventions include the cash grant recommended by Chersich et al (2016) above, or a health promotion approach tested by Tomlinson *et al* [306].

Clinical diagnosis and under-diagnosis of FAS: FAS can often be diagnosed in infancy (study 7) but is usually not recognised at all (study 2). To monitor the effectiveness of clinical detection, future FAS surveillance studies should routinely include a question about prior diagnosis. Under-recognition of FAS highlights a need for greater awareness and specific knowledge among health professionals.

Health professional education: The lack of a structured approach to screening for drinking, and lack of awareness among health professionals demand improved education both about risky drinking and about FAS and FASD. To ensure adequate coverage this must be provided both to undergraduates and in the form of ongoing medical

education. To adequately address undergraduate education at national level will require teaching syllabi to identify learning objectives for alcohol and FASD, and address both knowledge and skills.

Ongoing education on alcohol and FASD should receive a higher priority within provincial health departments. It should address the needs of a range of health professionals involved in prenatal and paediatric care - including medical, nursing, and allied health personnel. FARR provides an ongoing education on FASD, and the reach of this should be assessed.

Education around risky drinking should cover the relevant knowledge and skills related to enable participants to:

- Define risky drinking and binge drinking in men and women
- Specify risks of heavy drinking and binge drinking
- Use a screening tool to identify risky drinking
- Stratify level risk level
- Deliver an intervention according to level of risk
- Understand AEP in the context of embryological development
- Understand specific issues related to AEP and prevention of AEP, including the importance of contraception for risky drinkers, and a structured approach to addressing drinking in an antenatal and postnatal care context
- Be aware of other risk factors for FAS, and the need to address these simultaneously with alcohol use

Education around FASD should be adapted to the relevant professional grouping, but should cover:

- Prevalence of FAS and FASD, risk factors, and red flags for considering the diagnosis
- Classification of FASD
- Clinical diagnosis of conditions within the FASD spectrum, including a simple approach to dysmorphic and neurodevelopmental assessment
- Clinical implications and prognosis
- Early childhood intervention and other aspects of treatment
- Appropriate follow-up

Early child development: The findings of the prevalence surveys together with study 7 suggest that, within the Western and Northern Cape provinces, the approach to early child development target three levels: (1) Supporting parenting and early learning in all children (2) In PAE children, an additional focus on monitoring of development, and cessation of maternal alcohol use (3) Early diagnosis of P/FAS, in order to facilitate early developmental intervention, in the form of an appropriate 'package of care'. This very broad recommendation requires further disaggregation.

6.2 RECOMMENDATIONS FOR RESEARCH

There is a particular need for qualitative, translational and operational research in order to implement, and maximise the effectiveness of, appropriate interventions.

Monitoring of P/FAS prevalence: Prevalence surveys are cumbersome and costly undertakings, and should be carefully prioritised to enhance the value of the information generated. Geographical areas should be targeted if they are likely to be at high risk (for example, based on information on drinking practices or because they have similarities to sites with confirmed high FAS prevalence), but with sufficient doubt that a high prevalence of FAS cannot simply be assumed. In other words, if an area is known to have a high prevalence of risky drinking, and the population characteristics are similar to areas with high FAS prevalence, then the added benefit of a survey might not be large. However, results of a survey are often useful for flagging the problem and securing additional resources for FAS prevention in an area.

Some priorities areas for surveillance include:

- Cape Town: although the population of this city shares much in common with the rest of the Western Cape, including a relatively high prevalence of female binge drinking, the prevalence of FAS has not been documented in the metropole (with a population similar in number to the rest of the Western and Northern Cape provinces combined). Unlike other study sites, it also has a particularly high rate of poly-drug abuse.
- Other urban areas in South Africa, especially where there is evidence of binge-drinking being prevalent, and including the majority BSA population (in view of the findings of study 2)
- Specific sub-populations likely to be at high risk. Data from our and other studies suggest that children of HIV-positive women, and children in institutional or foster care are at potentially high risk.
- Follow-up surveys at intervention sites. In particular, it would be important to follow-up the De Aar site, where FAS awareness activities have been performed regularly since 2001.

- To date surveillance has been restricted to South Africa. The WHO Global Status Report on Alcohol and Health [6] has identified a high prevalence of risky drinking in other southern African countries, and there is a need to extend FAS surveillance operations.

FAS surveillance methods: Given the logistical complexities and costs of current FAS surveillance, there is clearly a need for less labour-intensive and more cost-effective methods. A variety of approaches should be assessed for broader implementation. Possibilities include: assessments of hospital records similar to the method described by Hymbaugh *et al* (2002) [161] and Moberg *et al* (2014) [159], photographic screening methods as outlined by Astley and Clarren (1996) [95] and Astley *et al* (2002) [285], or a method that involving screening by CHWs screening which O'Connor *et al* (2014) [307] found to be quite accurate in a Cape Town setting.

There have been considerable advances in imaging technology since the photographic screening methods were developed. It would be particularly useful to investigate as a screening tool the use of a cellphone app such as Face2Gene (https://www.face2gene.com/) which allows automated analysis of facial dysmorphology in conjunction with other input data.

Monitoring drinking: Inclusion of appropriate indicators of drinking will facilitate research to determine geographical and temporal trends in drinking among reproductive age and pregnant women. This can be linked with FAS prevalence data, which is likely to remain more fragmentary in the medium term, to better map the risk of FAS/FASD in South Africa and assess changes associated with interventions.

The last published national survey of drinking was performed 9 years ago. Follow-up surveys should ideally include more detailed information that would support intervention design, such as on drinking environments, norms and perceived norms, key risk factors, knowledge of drinking risks, and existence of stigma.

Universal interventions: Cost-effective approaches to alcohol-related health promotion need to be explored. Apart from CHW and traditional educational approaches, there is a need to assess the value of social media and cell-phone messaging, which are already being

introduced at scale for broader health promotion in the Western Cape [302].

Selective interventions: While selective interventions have shown benefit in local circumstances, broader introduction of SBIRT will bring attendant needs to refine interventions, and monitor their effectiveness. Further qualitative research is needed on how best to address the known drivers of binge drinking, AEPs, and ongoing drinking in pregnancy - in local circumstances.

There is a considerable literature on the benefits of ensuring that interventions are culturally appropriate [308–311] and research is warranted to optimise this aspect. In addition, interventions should aim to alter drinking behaviour not only of the client but also the partner and other members of the drinking network, and this should be included in design and monitoring. There is a need to assess how best to reduce re-establishment of binge-drinking after pregnancy.

Nutritional interventions: Although provision of a cash grant in pregnancy has clear advantages, it would be important to assess whether it is accompanied by increased drinking among risky drinkers in particular, given the possibility that they may be dependent on alcohol. Research is required on the role of, and target groups for, supplementation with a broader range of vitamins and micronutrients than currently offered.

Barriers to effective implementation: As with the introduction of measures to curb other perinatal public health problems, such as mother-to-child transmission of HIV, prevention of drinking in pregnancy requires a complex multistep process. It is inevitable that there will be challenges to effective implementation, and barriers will need to be reviewed and corrected on an ongoing basis.

Maternal mortality: The reasons for the high, and variable, maternal mortality rate detected needs to be assessed further, especially to delineate the extent to which this is explained by the concurrence of HIV infection and risky drinking, and how best it should be addressed.

Health professional education: Knowledge, skills and self-efficacy of students and professionals needs to be monitored.

Early child development: There is a need to assess maternal responses to diagnosis of a child with FAS, whether the child receives an approach package of care, and the proportion of women stopping drinking after diagnosis.

CHAPTER 7: SUMMATION

SUMMARY

This thesis builds a picture of FAS in South Africa in three dimensions. First it demonstrates that FAS is a public health problem affecting children, and their families and communities far more widely than was previously understood. It situates FAS as part of the broader problem of binge drinking in pregnancy, which may also have serious consequences for the mother, and her other children without obvious features of FAS. Second it describes mothers of children with FAS, their drinking practices and other risk factors across a range of localities. In particular it investigates for features that warrant consideration in preventive interventions. Finally, it evaluates a health promotion intervention conducted in two high risk communities.

At the start of the millennium FAS was known to be common in the winelands near the city of Cape Town, and this district has remained a focus of research and awareness-raising activity since. The concept arose that the high level of FAS in this area may have resulted directly from effects of centuries of exposure to the Dop system whereby labourers on the wine farms received a regular measure of alcohol as part of their remuneration. By extension, FAS might be particular to the Cape Winelands, and to the SAC population that historically comprised this workforce. However, surveys of drinking showed that, although most South African women do not drink, the practice of binge-drinking is quite widespread although not uniform around the country. The data are limited, and binge-drinking by women does not necessarily translate directly into a risk for FAS, but this does raise the counter possibility that FAS is a broader public health problem, either within the SAC population or more broadly in the South African population.

The thesis reports on prevalence surveys at six sites, all but one of which were outside the Cape Winelands district. Two were elsewhere in the Western Cape Province, and three were in the Northern Cape Province. The sites were predominantly low income communities in widely disparate geographical areas. Most comprised predominantly

SAC populations, but one included a sizeable township with a mainly BSA population. Although not selected for this purpose, the six study sites can reasonably be considered sentinel sites for the whole population of these two provinces, or at least for lower income communities, outside of metropolitan Cape Town.

The prevalence of FAS was high, near or above 5%, at all study sites. Collectively the surveys can therefore be interpreted to show that FAS is a large-scale public health problem for all similar communities throughout the Western and Northern Cape provinces. FAS is not restricted to the Cape Winelands. Although this does not discount the historical relevance of the Dop system, it is consistent with data showing more widespread binge-drinking that is no longer associated with the Dop.

The prevalence of FAS was highest in more rural areas, and in more isolated small towns, than elsewhere. This is consistent with findings in the Cape Winelands, and the USA, of a rural-urban gradient. Nonetheless, prevalence was high in the city surveyed. It is relevant that both rural and urban communities surveyed were of predominantly low SES, which has been shown to be a strong risk factor for FAS. South Africa is characterised by extreme income inequality, and has very high rates of poverty. The very high prevalence of FAS in South Africa studies compared to those in most other settings likely represents the combined effects of risky drinking together with other poverty-related factors, such as deficient nutrition, but perhaps also other factors associated with living in neglected communities.

While the prevalence was high in the mainly SAC communities at all sites assessed to date, it was not unique to this population. The high prevalence of FAS in a city township is indicative that FAS occurs also in the majority BSA population of the country. This township is one of the oldest in the country, and risky drinking practices in the community may result from prolonged exposure to the colonial economy since the 1870s. It may therefore not represent the situation in BSA populations in rural or more newly established urban communities elsewhere, given the traditional prohibitions on female drinking in this population. However it does indicate a need to assess the prevalence of FAS elsewhere in South Africa. It shows a need to

conceive of FAS as a South African problem, and to discard stereotypical notions of who is, or is not, at risk of the condition.

The latter point feeds into an additional finding – that none of the school entrants with FAS in the city population had been previously diagnosed. This points to a lack of awareness among health professionals and a lack of the necessary skills to make the diagnosis, and speaks to a need for nationwide standards regarding professional education regarding FAS, and regarding risky drinking more generally.

The longitudinal study of neurodevelopment showed that syndromic FAS cases often had developmental delay and could be diagnosed as FAS within the first year of life. By 5 years of age, these children on average had a GQ in the borderline range and the domains of practical reasoning and eye-and coordination were particularly compromised. However, both the controls and the non-syndromic children with prenatal alcohol exposure also exhibited faltering development, which was more marked in the PAE group. This indicates that the approach to early childhood development should target three levels: support of parenting and early learning in all children, an additional focus on monitoring development and cessation of maternal drinking in PAE children, and early diagnosis of FAS or developmental delay in order to facilitate further developmental support.

The study of maternal risk factors for FAS showed the expected regular binge-drinking pattern of drinking among case mothers. The minority of drinkers in the control group showed a similar but less regular pattern, and many more controls were drinking currently than reported drinking in the index pregnancy 7 years earlier. This is particular cause for concern because over two thirds of women did not plan their pregnancy, and on average women recognised pregnancy relatively late, at 3 months gestation.

Importantly, at all three sites, a proportion of women stopped drinking in pregnancy, and most at least reduced drinking. The study site expected to be most exposed to messaging about the risks of drinking in pregnancy also had the highest cessation rate, although it was difficult to conclude that these two aspects were necessarily related. A small minority of women reported increasing drinking in

pregnancy - the reasons for this were not explored in detail but most reported being very stressed in pregnancy.

Most women who stopped drinking in pregnancy restarted within months of giving birth, and more than a third of women were currently drinking and either not using contraception or pregnant, putting them at risk of an AEP. Nevertheless, stopping in pregnancy was associated with a higher chance of current abstinence. Few women considered themselves to have a current drinking problem, although a larger proportion were amenable to an intervention to reduce drinking.

The high prevalence of FAS, and of risky drinking in pregnancy, demands interventions to reduce AEPs. This can be achieved by reducing drinking in both reproductive age and pregnant women, and increasing contraception and family planning. The study findings suggest that pregnancy would be an opportune moment to intervene, since it is a time when women contemplate stopping drinking and also expect to be asked about alcohol use. However there is a need to reinforce the message again in pregnancy and at follow-up after birth, at which time there should be a focus on contraception and the risks of binge-drinking in particular. Other measures to reduce peri-conceptional drinking are also a priority.

A standardised approach to FAS prevention is required at provincial, and perhaps also at national level. There should be scope for some tailoring according to local circumstances, giving our findings that case women at different study sites had differences in a range of relevant variables, including: frequency of drink cessation, of smoking, and of underweight BMI.

Less obvious potential benefits of a successful intervention include decreased need for foster care, and decreased maternal mortality. In the 7 year interval between pregnancy and interview, we found that 12% of children with FAS required foster care (not previously described in South Africa), and on average 13% of mothers had died. The maternal mortality rate at one site of 29% was an outlier that is most likely the result of co-occurrence of alcohol and HIV, and requires further evaluation.

The pre-post study of a preventive intervention demonstrated a lower P/FAS prevalence, and reduced dysmorphology scores post-intervention compared to pre-intervention. In keeping with these findings, post-intervention mothers were found to have better knowledge of the risks of in-pregnancy drinking and a greater belief that this would change drinking practice. Although the pre-post study design prohibits definitive conclusions, the findings suggest that health promotion is effective, at least in the context of a high risk area with limited prior knowledge of FAS. The intervention was a multifaceted awareness-raising and educational approach which included media messaging and health professional education, but it was primarily driven by CHWs, who spoke to women in community forums, as well as in antenatal and other clinics. It is not possible to specify which aspect of the health promotion was most effective, but the study supports other local evidence for the value of CHWs in effecting alcohol-related behaviour change.

Some concluding remarks are warranted. FAS is a broader public health problem in South Africa than was previous thought. There is a need to extend FAS surveillance in a carefully targeted manner, with a focus on: follow-up in intervention sites, predominantly BSA communities with characteristics similar to that in which we demonstrated a high FAS prevalence, children in institutional or foster care, and HIV-exposed children. In addition, there is a need for national surveillance of drinking in pregnancy.

Despite the magnitude of the FAS problem in South Africa, measures to reduce alcohol-related harm have been restricted to broad policy approaches. There has been minimal focus, except in the media, on FAS or in-pregnancy drinking. I contend that the scale of the problem, certainly in the Western and Northern Cape provinces, but perhaps elsewhere in South Africa, requires a change. There is ample evidence from international research, augmented by local studies, that selective and educational interventions are effective and warranted. The current imperative is for implementation of measures to combat the occurrence of FAS, and to ameliorate it once it occurs.

SAMENVATTING

Deze thesis schetst een beeld van FAS (Fetaal Alcohol Syndroom) in Zuid Afrika in drie dimensies. In de eerste plaats illustreert het dat FAS een probleem is voor de volksgezondheid, wat kinderen, families en gemeenschappen op een veel grotere schaal affekteert dan voorheen gedacht. Het situeert FAS als onderdeel van het bredere probleem van binge drinking (consumptie van een grote hoeveelheid alcohol per drink-sessie) tijdens zwangerschap, wat ook ernstige gevolgen kan hebben voor de moeder zelf en haar andere kinderen die geen duidelijke kenmerken van FAS vertonen. Ten tweede beschrijft het drink praktijken en andere risicofactoren van moeders van kinderen met FAS in een verscheidenheid van locaties. In het bijzonder onderzoekt het factoren die overweging in preventieve interventies rechtvaardigen. Tot slot evalueert het een gezondheidspromotie interventie, uitgevoerd in twee hoog risico gemeenschappen.

Aan het begin van het millennium stond FAS bekend als frequent in de wijnstreek in de buurt van Kaapstad, en deze regio is sedertdien een focus van onderzoeks- en bewustmakingsacties gebleven. Het concept is ontstaan dat de hoge voorkomst van FAS in deze regio het directe gevolg was van eeuwenlange blootstelling aan het Dop-systeem, waarbij arbeiders op de wijn boerderijen een regelmatige hoeveelheid alcohol als deel van hun loon ontvingen. Voortvloeiend hieruit, onstond de notie dat FAS misschien wel typisch was voor de Kaapse Wijnlanden en de zuid-afrikaanse zogenaamde kleurling bevolking, die historisch gezien, deze arbeidskrachten uitmaakte.

Uit enquêtes over drinken is echter gebleken dat, hoewel de meeste Zuid-Afrikaanse vrouwen niet drinken, de praktijk van binge-drinken vrij wijdverspreid is, alhoewel niet uniform in het hele land. De gegevens zijn beperkt en binge-drinken door vrouwen is niet noodzakelijkerwijs rechtstreeks te vertalen in een risico voor FAS, maar anderzijds bestaat de mogelijkheid ook dat FAS een breder probleem mag zijn voor de volksgezondheid, hetzij binnen de kleurling gemeenschap of meer wijdverspreid in de algemene bevolking.

Deze thesis levert verslag over prevalentie enquêtes op zes locaties, waarvan allemaal behalve één buiten het Kaapse Wijnland district

gelegen waren. Twee waren in andere regios van de West-Kaap provincie en drie in de Noord-Kaap provincie. De locaties waren overwegend in laagbetaalde gemeenschappen in sterk uiteenlopende geografische gebieden. De meerderheid bestonden uit overwegend kleurling populaties, maar een area sloot ook een omvangrijk stadsgebied ("township") in met een voornamelijk zwarte bevolking. Hoewel niet geselecteerd voor dit doel, kunnen de zes studieplaatsen redelijkerwijs beschouwd worden als vertegenwoordigend voor de gehele bevolking van deze twee provincies, of ten minste toch voor de lage-inkomen gemeenschappen, buiten de metropool van Kaapstad.

De prevalentie van FAS was hoog bij alle studieplaatsen, in de buurt van of boven de 5%. Collectief kunnen de enquêtes dus worden geïnterpreteerd om aan te tonen dat FAS een grootschalig volksgezondheidsprobleem is voor alle gelijkaardige gemeenschappen in de West- en Noord-Kaap provincies en dat FAS niet beperkt is tot de Kaapse Wijnland streek. Hoewel dit geen afbreuk doet aan het historisch belang van het Dop-systeem, strookt het met de bevinding van meer wijdverspreid binge-drinken, dat niet langer gekoppeld is aan de Dop.

De prevalentie van FAS was het hoogst in de meer landelijke gebieden en in meer geïsoleerd kleine steden, dan elders. Dit komt overeen met vorige bevindingen van een landelijk-stedelijke gradient, beide in de Kaapse Wijnland streek en in de Verenigde Staten van Amerika. Toch was de prevalentie in de stad ook hoog. Het is relevant dat zowel de landelijke als stedelijke gemeenschappen in de studie van overwegend lage socio-economische status waren, aangezien dit bekend is om een sterke risicofactor te zijn voor FAS. Zuid-Afrika wordt gekenmerkt door extreme inkomensongelijkheid en heeft zeer hoge voorkomst van armoede. De zeer hoge prevalentie van FAS in Zuid-Afrika studies vergeleken met deze in meeste andere omgevingen vertegenwoordigt naar alle waarschijnlijkheid de gecombineerde effecten van riskant drinken samen met andere armoede-verwante factoren, zoals gebrekkige voeding, maar misschien ook andere factoren geassocieerd met het leven in verwaarloosde gemeenschappen.

Terwijl de prevalentie vooral hoog was onder de kleurling gemeenschappen die in deze locaties onderzocht werden, was het niet

uniek voor deze bevolkingsgroep. De hoge prevalentie van FAS in het onderzochte township is een indicatie dat FAS ook voorkomt onder de zwarte bevolking die de meerderheid uitmaakt in het land. Dit township is een van de oudste in het land, en riskante drink praktijken in deze gemeenschap kan voortgevloeid zijn uit langdurige blootstelling aan de koloniale economie sinds de jaren 1870. Dit gedrag is niet noodzakelijk vertegenwoordigend voor zwarte gemeenschappen in plattelandse of meer recent opgerichte stedelijke gebieden elders, gegeven het traditionele verbod op drinken door vrouwen in deze gemeenschappen. Het duidt echter wel de noodzaak aan om de prevalentie van FAS elders in Zuid-Afrika te onderzoeken en om FAS als een Zuid-Afrikaans probleem te beschouwen en weg te bewegen van stereotiepe opvattingen over wie wel of niet het risico loopt om het te ontwikkelen.

Dit laatste punt sluit aan bij een additionele bevinding, namelijk dat, in de stedelijke gemeenschap, geen enkele van de schoolgaande deelnemers met FAS voorheen als zulks gediagnosticeerd was. Dit wijst op een gebrek aan bewustzijn en een gebrek aan de nodige diagnostische vaardigheden onder gezondheidszorg personeel, en spreekt tot een behoefte aan land-wijde normen voor beroepsopleiding ten aanzien van FAS en riskant drinken meer in het algemeen.

De longitudinale neurologische ontwikkelingsstudie demonstreerde dat FAS gevallen vaak vertraging in de ontwikkeling vertoonden en dat de diagnose van FAS binnen het eerste levensjaar gemaakt kon worden. Op 5- jarige ouderdom, hadden deze kinderen een gemiddeld ontwikkelingsquotient in het borderline bereik en vooral de domeinen van praktisch redeneren en oog-hand coördinatie waren aangetast. De studie toonde echter ook aan dat de controles alsook de kinderen met prenatale alcohol blootstelling maar zonder FAS-tekens, ook haperende ontwikkeling vertoonden (meer uitgesproken in de groep met blootstelling). Dit geeft aan dat de benadering tot ontwikkeling in de vroege kinderjaren op drie niveaus gericht moet worden: ondersteuning van ouderlijke vaardigheden en vroege leergelegenheden voor alle kinderen, met een extra focus op het moniteren van de ontwikkeling en het stopzetten van drinken door de moeder voor kinderen met prenatale alcohol blootstelling, en vroege

diagnose van FAS of ontwikkelingsachterstand teneinde verdere ontwikkelingssteun aan te bieden.

De studie van maternele risicofactoren voor FAS toonde het verwachte regelmatige binge-drinken patroon. Slechts een minderheid van vrouwen zonder aangetaste kinderen rapporteerde een soortgelijk, maar minder regelmatig drink-patroon maar heel wat meer van hen dronken momenteel vergeleken met alcohol gebruik tijdens de index zwangerschap 7 jaar tevoren. Dit is een bijzondere reden tot zorg omdat meer dan tweederde van vrouwen een zwangerschap niet vooraf beplannen en dat ze een zwangerschap vaak relatief laat herkennen, gemiddeld slechts op 3 maanden.

Belangrijk is dat, op alle drie locaties, een deel van de vrouwen ophielden met drinken tijdens de zwangerschap, en dat meesten hun alcohol inname ten minste verminderden. De studiegroep met de hoogste kans om blootgesteld te zijn aan boodschappen over de risico's van drinken tijdens zwangerschap, had ook het hoogste percentage van vrouwen die ophielden maar het was moeilijk om te bewijzen dat deze twee aspecten noodzakelijkerwijs verband hielden. Een kleine minderheid van vrouwen meldde dat hun alcohol inname toenam tijdens zwangerschap - de redenen hiervoor waren niet onderzocht in detail, maar meesten meldden dat ze zeer veel spanning hadden tijdens de zwangerschap.

De meerderheid van vrouwen die gestopt waren met drinken tijdens de index zwangerschap waren weer gestart binnen maanden na de bevalling, en meer dan een derde van hen gebruikte alcohol op het ogenblik, terwijl ze ofwel weer zwanger waren of geen contraceptie gebruikten, en dus het gevaar liepen van een zwangerschap met alcohol-blootstelling. Toch was stoppen tijdens de index zwangerschap geassocieerd met een hogere kans op huidige onthouding. Weinig vrouwen beschouwden zichzelf als iemand met een huidig drankprobleem, maar een groter aantal waren vatbaar voor een interventie om drinken te verminderen.

De hoge prevalentie van FAS en van riskant drinken tijdens zwangerschap, vraagt om interventies ter voorkoming van alcohol-blootgestelde zwangerschappen. Dit kan worden bereikt door het verminderen van drinken door vrouwen van reproductieve ouderdom en zwangere vrouwen, en het verbeteren van contraceptie gebruik en

gezinsplanning. De studie bevindingen suggereren dat zwangerschap een gunstige gelegenheid kan zijn voor interventie omdat het een periode is wanneer vrouwen overwegen om op te houden met drinken en ook verwachten om ondervraagd te worden over hun alcohol gebruik. Het is echter noodzakelijk om de boodschap opnieuw te versterken tijdens de zwangerschap en bij de follow-up na de geboorte, op welk moment er ook klem moet worden gelegd op contraceptie en de risico's van binge-drinken in het bijzonder. Andere maatregelen ter vermindering van het peri-conceptuele drinken zijn ook een prioriteit.

Een gestandaardiseerde aanpak voor het voorkomen van FAS is vereist op provinciaal en misschien ook op nationaal niveau. Er moet ruimte zijn om aanpassingen te maken volgens plaatselijke omstandigheden, gezien onze bevindingen van verschillen in een aantal relevante variabelen onder vrouwen op de verschillende studieplaatsen, onder andere verschillen in de frequentie van stopzetting van alcohol inname, roken en ondergewicht.

Minder voor de hand liggende potentiële voordelen van een succesvolle interventie sluit een verminderde behoefte aan pleegzorg in alsook een vermindering in moedersterfte. In het 7 jaar interval tussen de index zwangerschap en het interview vonden we dat 12% van de kinderen met FAS pleegzorg vereisten (nog niet voorheen beschreven in Zuid-Afrika), en dat gemiddeld 13% van de moeders reeds overleden waren. De 29% moedersterfte op één plaats was een uitschieter die zeer waarschijnlijk het resultaat was van de kombinatie van alcohol en HIV, en dit vereist een grondiger evaluatie.

De pre-post vergelijkende studie van een preventieve interventie toonde een lagere FAS prevalentie en minder ernstige dysmorfologie scores na de interventie ten opzichte van voor de interventie. In overeenstemming hiermee, bleken de moeders na de interventie een betere kennis te hebben van de risico's van drinken tijdens zwangerschap en een grotere overtuiging dat drink praktijk kan veranderen. Hoewel het ontwerp van de pre-post studie geen definitieve conclusies mogelijk maakt, suggereren de bevindingen dat gezondheidsbevordering effectief is, ten minste in het kader van een hoog risico gebied met beperkte voorkennis van FAS. De interventie bestond uit een veelzijdige bewustmakings- en educatieve aanpak met onder andere gebruik van media boodschappen en onderricht voor

professioneel gezondheidszorg personeel, maar het was vooral gedreven door gemeenschapsgezondheidswerkers (leken) die vrouwen toespraken in gemeenschapsforums, evenals in prenatale en andere klinieken. Het is niet mogelijk om te speculeren welk aspect van de interventie meest effectief was, maar de studie ondersteunt andere lokale bevindingen aangaande de waarde van gemeenschapsgezondheidswerkers in het bereiken van verandering in alcohol-verwant gedrag.

Sommige slotopmerkingen zijn gerechtvaardigd. FAS is een breder probleem voor de volksgezondheid in Zuid-Afrika dan voorheen gedacht. FAS-onderzoek behoort uitgebreid te worden op een doelgerichte manier, met een focus op: follow-up na interventie, overwegend zwarte gemeenschappen met eigenschappen die vergelijkbaar zijn met die waarin we een hoge prevalentie van FAS vonden, kinderen in institutionele zorg of pleegzorg en HIV-blootgestelde kinderen. Daarnaast is er behoefte aan monitering van drinken tijdens zwangerschap op nationaal niveau.

Ondanks de omvang van het probleem van FAS in Zuid-Afrika, zijn maatregelen ter vermindering van alcohol-verwante schade tot dusver beperkt gebleven tot brede beleidsbenaderingen en er is, behalve in the media, minimale aandacht gegeven aan FAS of alcohol gebruik tydens zwangerschap. Ik beweer dat de omvang van het probleem, zeker in de West- en Noord-Kaap provincies maar misschien ook elders in Zuid-Afrika, een verandering vereist. Er is voldoende bewijs, gebaseerd op internationaal onderzoek aangevuld met lokale studies, dat selectieve en educatieve interventies effectief en gerechtvaardigd zijn. Het is dringend noodzakelijk dat maatregelen geimplementeerd worden ter bestrijding van de ontwikkeling van FAS en ter verbetering van FAS zodra de schade gevestigd is.

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ANNEXURES – OTHER PUBLICATIONS

ANNEXURE 1 – STUDY 6

Davies L, Dunn M, Chersich M, **Urban M**, Chetty C, Olivier L, Viljoen D. Developmental Delay of Infants and Young Children with and without fetal alcohol spectrum disorder in the Northern Cape Province, South Africa. *African Journal of Psychiatry* 2011; *14: 299-305.*

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Developmental delay of infants and young children with and without fetal alcohol spectrum disorder in the Northern Cape Province, South Africa

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Abstract
Objective: To describe the extent and nature of developmental delay at different stages in childhood in a community in South Africa, with a known high rate of Fetal Alcohol Spectrum Disorder (FASD). **Method:** A cohort of infants, clinically examined for FASD at two time periods, 7-12 months (N= 392; 45 FASD) and 17-21 months of age (N= 83, 35 FASD) were assessed using the Griffiths Mental Developmental Scales (GMDS). **Results:** Infants and children with FASD perform worse than their Non-FASD counterparts over all scales and total developmental quotients. Mean quotients for both groups decline between assessments across subscales with a particularly marked decline in the hearing and language scale at Time 2 (scores dropping from 110.6 to 83.1 in the Non-FASD group and 106.3 to 72.7 in the FASD group; P=0.004). By early childhood the developmental gap between the groups widens with low maternal education, maternal depression, high parity and previous loss of sibling/s influencing development during early childhood. **Conclusion:** The FASD group show more evidence of developmental delay over both time points compared to their Non-FASD counterparts. Demographic and socio-economic factors further impact early childhood. These findings are important in setting up primary level psycho-educational and national prevention programmes especially in peri-urban communities with a focus on early childhood development and FASD.

Keywords: Developmental Delay; Fetal Alcohol Syndrome (FAS); Griffiths Mental Developmental Scales (GMDS)

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Introduction

Developmental delays in early childhood are often associated with later more permanent neurocognitive deficits. Identifying these delays during infancy is complicated. However, their early detection provides important opportunities for invaluable referrals and intervention, significantly decreasing secondary disabilities in later childhood. Without early detection and intervention for developmental delays the vast majority of children with delays will experience some degree of learning disability limiting their life opportunities.[1] The most common cause of developmental delay worldwide is FAS (Fetal Alcohol Syndrome).[2] Some of the highest prevalence rates of FASD (Fetal Alcohol Spectrum Disorder) have been documented in South Africa, affecting up to 10.9 per 1000 children in heavily affected areas.[3-6] Few studies have assessed developmental delay within impoverished communities in South Africa. Fewer still, have focused on the impact of prenatal alcohol exposure on early childhood development.

FAS is the most severe disorder within the Fetal Alcohol Spectrum, the umbrella term encompassing all disorders associated with prenatal alcohol exposure including, full FAS, Partial FAS and the subtler, often misdiagnosed, behavioural and neurodevelopmental aspects of Alcohol Related

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Neurodevelopmental Disorder (ARND) and Alcohol Related Birth Defects (ARBD).[7] Previous studies document cognitive dysfunction amongst children prenatally exposed to alcohol as being in the borderline range with many showing difficulties in solving problems, shifting attention between tasks, poor memory recall and executive functioning.[8-15] Findings from a study conducted in South Africa on children aged 7 years of age suggests that children with a FASD diagnosis perform lower on higher order cognitive competencies.[16] About two thirds of children with FASD require special services for learning problems in schools, yet limited special service resources are available in South Africa.[17] Public sector psychiatric services are poorly developed in smaller towns and rural areas in South Africa while the child and adolescent sub-speciality remains chronically under-resourced.[18] Further, the integration of mental health care services within primary health care lags.[19] With scarcity of psychiatric specialists in peri-urban communities, limited child mental health services are provided by primary health care staff. Also, there is very little integration of psychiatric services between the departments of health, education or social services. Although previous studies relating to delays during childhood differ in their sampling, research designs and measurements, they consistently confirm the existence of an association between socio-economic circumstances and early development.[20-25] Adverse conditions in developing countries with high rates of poverty and maternal depression after childbirth, are high and compromise childhood developmental outcomes. A key contributor to overall child wellbeing is maternal mental health with maternal depression impacting the early mother-infant relationship and overall child development.[26-29] The bonding relationship said to commence immediately after birth is greatly affected by the child's state as well as the mothers wellbeing. Better infant developmental outcomes have been linked to an increased sense of security in the key attachment relationship. Much is known about the cognitive effects of prenatal alcohol exposure, yet little is known of the early developmental delays and mediating factors amongst infants and young children. This lack of information may partly be attributed to the difficulties in making a FASD diagnosis in infancy.[30] The aim of the present study was to describe the extent and nature of developmental delay over two time periods (7-12 months and 17-29 months) and highlight the impact of FASD and external variables on early childhood development as measured by the infant scales of the GMDS, with important implications for sub specialities within psychiatry.

Methods

Sample

The sample consisted of a cohort of infants born in a one year period between 2002 and 2003 in the public hospital in De Aar. Infants were identified from birth records collected from the hospital (n=500). Potential participants, living in the town (many women in surrounding rural areas deliver in De Aar and return home thereafter), were invited to participate. Of the initial larger sample of infants (younger than 12 months) who received a clinical diagnosis at Time 1 less than half returned for their second assessment during early childhood (older than 12 months) at Time 2. Sample attrition was anticipated due to the longitudinal nature of the study and the characteristics of the population. However, it was further complicated by; the passive follow up of Non-FASD children, families moving out of town, refusal to take part in the second assessment and deaths of mothers or children.

Procedure

Once permission had been obtained from the Department of Health to access birth record data, potential participants were visited at their homes and invited to participate in the study. Infants whose parents/guardians consented to participate received a clinical examination and a developmental assessment. Mothers of infants with possible prenatal exposure were actively followed up and a maternal interview and Beck Depression Inventory was administered.

Identification of FASD group

Two specialist clinicians with dysmorphology training used the Institute of Medicine (IOM) criteria, to diagnose FASD amongst infants and children at Time 1 and 2.[7] A FAS diagnosis was made when infants and children had the characteristic facial phenotype, of small palpebral fissures, midface hypoplasia, smooth philtrum and/or thin vermillion border; with the presence of growth deficiency (on or below the 10th percentile for height and/or weight and/or head circumference) and observed neurological abnormalities. A PFAS diagnosis required at least two of the three facial features, as stated above, with growth deficiency and the presence of neurological abnormality. The clinical diagnosis of FAS, but not PFAS is considered distinctive even in the absence of a history of maternal alcohol consumption in pregnancy.[31,32] The FASD group for this study was defined as the combination of FAS and PFAS diagnosed cases. Infants without a confirmed FAS or PFAS diagnosis formed the Non-FASD comparison group. It is anticipated that some infants in the Non-FASD group had subclinical effects of prenatal alcohol exposure, which may have influenced the developmental performance, but were insufficient to warrant a clinical FASD diagnosis.

Developmental Assessment

The level of cognitive and motor development of infants and children, at both time periods, was assessed using the GMDS.[33,34] These scales, developed in the United Kingdom, have been extensively used in South Africa.[35-48] They show good test-retest reliability and are able to predict long term development.[49] The first five scales assess development from infancy to middle childhood (age 8) with the higher order, sixth scale included at three years of age. Items of the GMDS were adapted for the population and test instructions were translated into Afrikaans and then back translated. Translators were used with caregivers and children who were Xhosa speaking.

Due to the age of the sample being younger than 2 years, general quotients obtained from the subscales were used, as was accepted practise at the time of the study. Measurements for children older than 2 years are now based on percentiles, due to their higher validity.[50] Quotients for each subscale were derived independently and averaged to give a total developmental quotient. Each subtest is uniquely scaled, the mean (μ=100) and standard deviations of 16 were used. Higher scores indicate better performance. If developmental indices could not be determined due to low raw test scores an index score of 50 (the lowest standard score) was assigned. Using the GMDS developmental delay categories, we define developmental delay amongst all of the subscales and total developmental quotient as 2 standard deviations below the expected mean (</=68) and scores of between 1 and 2 standard deviations below the mean (69-83) were described as borderline developmental delay.

Table I: Characteristics of study participants in De Aar, South Africa by infant FASD status

Variables	*Non-FASD n/N (%)*	*FASD n/N (%)*	*P**
Maternal Variables			
Age, years			
15-19	46/348 (13)	1/43 (2)	
20-24	110/348 (32)	4/43 (9)	
25-29	86/348 (25)	9/43 (21)	
30-34	77/348 (22)	21/43 (49)	
35-60	29/348 (8)	8/43 (19)	<0.001**
Ethnicity			
Black	111/353 (31)	6/45 (13)	
Mixed ancestry	241/353 (68)	39/45 (87)	
Other	1/353 (0.3)	0/45	0.039*
Marital status			
Living together	26/345 (8)	10/45 (22)	
Married/Engaged	79/345 (23)	8/45 (18)	
Single	240/345 (70)	27/45 (60)	<0.006*
Maternal body mass index			
18.5-24.9	3/30 (10)	8/35 (23)	
25-29.9	20/30 (67)	21/35 (60)	
≥30	6/30 (20)	3/35 (9)	0.268
Level of education			
Incomplete primary school	30/325 (9)	15/40 (38)	
Primary school completed	32/325 (10)	10/40 (25)	
Incomplete high school	166/325 (51)	14/40 (35)	
High school completed	92/325 (28)	1/40 (3)	
Tertiary	5/325 (2)	0/40	<0.001**
Maternal occupation			
Unemployed	267/343 (78)	39/45 (87)	
Temporary employed	29/343 (9)	3/45 (7)	
Full time employed	47/343 (14)	3/45 (7)	0.354
Parity			
1	131/343 (38)	3/45 (7)	
2	103/343 (30)	12/45 (27)	
3	54/343 (16)	15/45 (33)	
4+	55/343 (16)	15/45 (33)	<0.001**
Death of a child			
Yes	43/340 (13)	15/45 (33)	<0.001**
Maternal alcohol use during pregnancy†			
1 week	6/39 (15)	1/36 (3)	
2-3 weeks	2/39 (5)	5/36 (14)	
Every week	5/39 (13)	25/36 (69)	
Never	26/39 (67)	5/36 (14)	<0.001**
Maternal depression (Becks Inventory Score)			
Normal (0-10)	72/309 (23)	8/40 (20)	
Mild (11-19)	93/309 (30)	4/40 (10)	
Clinical (20-29)	80/309 (26)	7/40 (18)	
Moderate (30-39)	42/309 (14)	10/40 (25)	
Severe (40+)	22/309 (7)	11/40 (28)	<0.001**
Infant Variables			
Gender			
Male	178/354 (50)	17/45 (38)	
Female	176/354 (50)	28/45 (62)	0.114
Low birth weight (<2.5kg)			
<2.5kg	48/326 (15)	26/42 (62)	
≥2.5kg	278/326 (85)	16/42 (38)	<0.001**
FASD diagnosis	347/392 (89)	45/392 (12)	

Note: FASD=Fetal Alcohol Spectrum Disorder; † = average number of weeks mother drank during pregnancy; p<0.05*; p<0.001**

Maternal Interview

Maternal interviews were used to measure demographic, socio-economic variables and alcohol use within groups. Trained interviewers completed a structured questionnaire with participating mothers, previously developed and tested on local populations.[51] History of alcohol consumption was acquired from mothers of FASD children and an equal number of controls using a using a timeline follow-back method.[52,53] Shorter interviews were used with guardians if mothers were deceased or untraceable. The Beck Depression Inventory was administered to mothers of participating infants to assess cognitions associated with depression.[54,55] Participating mothers received an honorarium in the form of a food voucher and a laminated photo of themselves and their child.

Referrals to local professionals and services, including speech and hearing therapists, occupational therapists and physiotherapists were made with infants and children who presented with FASD or other developmental delays. Other medical conditions detected during clinical examinations of the infants and children were referred to local and regional medical services, as required. Mothers with depressive symptoms were referred to the psychiatric nurse for evaluation and a support group, while those with alcohol dependence were linked with specialist programmes being run through local non-governmental organisations.

The study was nested within a larger prevention study that was conducted in De Aar and the neighbouring town of Upington. The focus of this study was on the De Aar sample. The University of the Witwatersrand Research Committee study reviewed and approved the project (M01-11-20).

Statistical analysis

Clinical data, GMDS mean quotients, infant characteristics, maternal demographic and socio-economic variables were analysed using Intercooled Stata 10.0 (Stata Corporation, College Station, TX). Univariate comparisons for categorical variables were tested using a chi-square test or chi-square test for trend. For continuous variables, the Student's t test and Wilcoxon rank-sum test were used for comparing data with normal and non-normal distributions, respectively. Because standard growth curves were not available for children in South Africa, Centres for Disease Control growth reference curves were used.

Results

About 10% of infants examined at 7-12months of age (n=392) were diagnosed with either FAS or PFAS, forming the FASD group (45/392). Of those, 21% (81/392) returned for their second assessment with 35 diagnosed with FASD during early childhood. More than two thirds of the sample (n= 398, 70.4%) were of mixed ancestry, with 29.4 % classified as black (117/398) (Table I). Demographic data in Table I indicates that almost two thirds of infants (26/42; 61.9%) in the FASD group were of low birth weight (<2.5kg). Mothers of children with FASD were more likely to be older (P<0.001) and single (P<0.006), although most mothers in the community were unmarried. Particularly low levels of education were reported amongst mothers of FASD children, with 35% having no formal secondary schooling. Fifteen of the mothers within the FASD group (33.3%) had more than four children with the same percentage of mothers having lost a child. Twenty five mothers with a FASD diagnosed child (69%) reported drinking alcohol, on average, every week during their pregnancy. Finally, depression was very common amongst women in the community, with 27.5% of the mothers in the FASD group (11/40) having severe depression, and 30% of the mothers in the Non-FASD group (93/309) showing mild depression.

Student t tests were conducted to compare the developmental means between groups over the GMDS subscales. Table II describes the descriptive statistics between groups obtained for each subscale, as well as the total developmental quotient over both time points. Total developmental quotients of the FASD group were significantly lower than the Non-FASD group at both Time 1 (mean=97.7, SD =14; P<0.001) and Time 2 (mean=75.1, SD=14.7; P<0.001). All subscale mean scores for the FASD group were lower than their counterparts at Time 1, with 4 of the 5 subscales showing significant differences, with gross motor functioning being the most marked. No significant differences were found between infant groups on the eye and hand subscale (P=0.37). Both groups performed within the average to above average range (90-119) over all scales on the GMDS categories at Time 1. By Time 2 greater differences between groups emerged. Means at Time 2 dropped over all subscales for both groups when compared to Time 1, although the FASD continue to perform significantly worse over all domains, dropping in their performance from average or above average to within the borderline range (70-84) for all scales. By Time 2 the greatest decrease in performance for both groups occurs on the hearing and language subscale.

Table II: Mean developmental quotients and standard deviations comparing infants with and without fetal alcohol spectrum disorder

GMDS Subscales Mean (SD)	*Time 1 7-12 months*			*Time 2 17-29 months*		
	Non-FASD (n=347)	*FASD (n=45)*	*P**	*Non-FASD (n=48)*	*FASD (n=35)*	*P**
Locomotor	100 (13.4)	89.8 (17.9)	<0.001**	90.1 (15.4)	78.3 (17.6)	<0.001**
Personal-Social	109.4 (15.7)	102.3 (16.7)	0.004*	97.8 (18.8)	79.0 (20.9)	<0.001**
Hearing - Language	110.6 (11.4)	106.3 (12.7)	0.02*	83.1 (15.6)	72.7 (16.7)	0.004*
Eye - Hand Coordination	100.9 (15.7)	98.6 (18.4)	0.37	86.8 (13.5)	75.4 (18.3)	<0.001**
Performance	96.9 (14.5)	92.3 (19.4)	0.05*	82.3 (14.5)	70.6 (16.6)	<0.001**
Total developmental quotient	103.8 (11.2)	97.7 (14.0)	<0.001**	87.8 (12.1)	75.1 (14.7)	<0.001**

Note: GMDS=Griffiths Mental Developmental Scales; SD=Standard deviation; FASD=Fetal Alcohol Spectrum Disorder, p<0.05*; p<0.001**

Table III: Association between maternal and infant characteristics on developmental delay in infancy and early childhood regardless of fetal alcohol syndrome diagnosis

Variables	*Time 1 n/N (% delayed)*				*Time 2 n/N (% delayed)*			
Maternal Variables	*Locomotor*	*Personal-Social*	*Performance*	*Total DQ*	*Locomotor*	*Personal Social*	*Performance*	*Total DQ*
Age, years								
20-24	3/114 (3)	1/114 (1)	3/114 (3)	0/114	3/17 (18)	1/17 (6)	3/17 (18)	2/17 (12)
25-29	2/93 (2)	1/93 (1)	2/93 (2)	1/93 (1)	2/19 (11)	2/19 (11)	3/19 (16)	2/19 (11)
30-34	1/97 (1)	0/97	5/96 (5)	1/97 (1)	6/29 (21)	8/29 (28)	10/29 (35)	7/29 (24)
35-60	1/35 (3)	1/35 (3)	3/34 (9)	1/35 (3)	1/11 (9)	2/11 (18)	2/11 (18)	3/11 (27)
P*	0.753	0.523	0.176	0.491	0.747	0.278	0.398	0.518
Marital status								
Living together	3/36 (8)	1/36 (3)	2/36 (6)	1/36 (3)	2/6 (33)	2/6 (33)	2/6 (33)	2/6 (33)
Married/Engaged	0/86	0/86	3/84 (4)	0/86	2/18 (11)	4/18 (22)	4/18 (22)	5/18 (28)
Single	4/266 (2)	2/266 (1)	8/266 (3)	2/266 (1)	9/55 (16)	9/55 (16)	14/55 (26)	9/55 (16)
P*	0.006*	0.278	0.724	0.278	0.445	0.557	0.863	0.410
Level of education								
No primary school	1/45 (2)	1/45 (2)	5/45 (11)	1/45 (2)	2/15 (13)	3/15 (20)	4/15 (27)	4/15 (27)
Primary school completed	2/42 (5)	1/42 (2)	1/42 (2)	1/42 (2)	5/13 (39)	5/13 (39)	6/13 (46)	5/13 (39)
No high school	3/179 (2)	1/179 (1)	5/178 (3)	1/179 (1)	3/36 (8)	4/36 (11)	7/36 (19)	4/36 (11)
High school completed	1/92 (1)	0/92	2/92 (2)	0/92	0/8	0/8	1/8 (13)	0.8
P*	0.680	0.513	0.073	0.513	0.032*	0.073	0.223	0.062
Parity								
1	2/133 (2)	1/133 (1)	2/133 (2)	1/133 (1)	2/14 (14)	0/14	1/14 (7)	0/14
2	2/115 (2)	1/115 (1)	3/114 (3)	1/115 (1)	2/21 (10)	2/21 (10)	6/21 (29)	3/21 (14)
3	2/68 (3)	0/68	3/68 (4)	0/68	6/23 (26)	9/23 (39)	10/23 (44)	8/23 (35)
4+	1/70 (1)	1/70 (2)	5/69 (7)	1/70 (1)	3/20 (15)	4/20 (20)	3/20 (15)	5/20 (25)
P*	0.892	0.818	0.172	0.818	0.505	0.015*	0.054*	0.065
Death of a child								
Yes	0/58	0/58	4/58 (7)	1/57 (2)	5/19 (26)	7/19 (37)	5/19 (26)	7/19 (37)
P*	0.260	0.463	0.111	0.376	0.206	0.015*	0.848	0.028*
Maternal alcohol use during pregnancy†								
1-3 weeks	1/14 (7)	1/14 (7)	1/14 (7)	1/14 (7)	2/6 (33)	2/6 (33)	4/6 (67)	3/6 (50)
Every week	3/30 (10)	3/30	3/30 (10)	1/30 (3)	5/19 (26)	5/19 (26)	6/19 (32)	6/19 (32)
Never	0/30	1/30 (3)	0/30	0/30	2/11 (18)	4/11 (36)	3/11 (27)	4/11 (36)
P*	0.219	0.381	0.219	0.381	0.774	0.836	0.227	0.715
Maternal depression								
Normal (0-10)	1/80 (1)	1/80 (1)	3/80 (4)	0/80	2/14 (14)	2/14 (14)	3/14 (21)	3/14 (21)
Mild (11-19)	0/97	0/97	1/97 (1)	1/97 (1)	1/14 (7)	1/14 (7)	2/14 (14)	1/14 (7)
Clinical (20-29)	3/87 (4)	1/87 (1)	2/87 (2)	1/87 (1)	2/16 (13)	2/16 (13)	6/16 (38)	2/16 (13)
Moderate (30-39)	0/52	0/52	3/52 (6)	0/52	1/13 (8)	2/13 (15)	2/13 (15)	2/13 (15)
Severe (40+)	2/33 (6)	1/33 (3)	4/33 (12)	1/33 (3)	5/12 (42)	3/12 (25)	4/12 (33)	5/12 (42)
P*	0.094	0.502	0.049*	0.543	0.109	0.784	0.493	0.206
Infant Variables								
Low birth weight								
<2.5kg	4/74 (5)	3/74 (4)	4/74 (5)	3/74 (4)	4/38 (11)	6/28 (21)	7/38 (18)	7/28 (25)
P*	0.014	<0.001**	0.178	<0.001**	0.237	0.553	0.185	0.342

Note: Time 1= 7-12 months of age, Time 2= 17-29 months of age; Total DQ= Total developmental quotient; † = average number of weeks mother drank during pregnancy; p<0.05*; p<0.001**

Table III presents the maternal characteristics associated with developmental delay of the whole population regardless of FASD diagnosis. At Time 1 relationships between marital status and lower locomotor scores (P<0.006) emerged, while low birth weight was significantly associated with delays on the personal and social (P<0.001) and total developmental quotient (P<0.001). Maternal depression further influenced the performance scale (P<0.049). With age, more socio-economic variables contribute to early childhood delay. Low maternal education (P=0.032) is associated with delayed scores on the locomotor subscale during early childhood, while having a higher parity and having lost a sibling (P<0.015) shows delay on the personal and social and performance scales. Gross motor functioning and overall performance are the only two subscales to be consistently influenced by socio-economic variables at both time points, although variation of the socio-economic variable in question exists.

Discussion

Although socio-economic factors like poverty and prenatal maternal alcohol consumption place children at a greater risk for developmental delay, the risk to a larger extent is dependent upon the micro-environment of the child.[56] Overall results from the study indicate that the FASD group show more developmental delay when compared to their Non- FASD counterparts over all developmental subscales. Aside from these anticipated delays associated with prenatal alcohol exposure, the FASD group performed relatively well during their infant assessment, however, showed marked delay during early childhood. With age, the developmental delay between groups becomes more evident and the apparent influence of socio-economic factors more marked. Our findings concur with previous research showing that children from low-income families tend to score within the normal range on cognitive assessments during early infancy but when they remain in disadvantaged environments for the first two years of life, all developmental domains become more significantly deprived.[57-60] Regardless of prenatal alcohol exposure, social factors have been shown to be amongst the strongest predictors of poor developmental outcome with children living in poverty at greater risk for cognitive delays.[61-63]

Results from the current study suggest that maternal marital status is linked to delayed gross motor development during infancy. While by early childhood, levels of maternal education play a larger role. Although specific income indicators were not collected in the current study, maternal level of education and occupation are generally correlated with income.[63] Most researchers concur that maternal education levels are amongst the most reliable predictors of childhood development with similar associations between low maternal educational levels and gross motor functioning been reported in a study amongst black South African children 13 to 16 months of age.[48] On the other hand, researchers using the Bailey Scales of Infant Development failed to find a link between low maternal education levels, their findings suggest that the quality of the home environment affects the gross motor delay of low birth weight infants aged 18 months to 5 years.[64] The current study identified links between high parity and the death of a sibling with delay over developmental scales during early childhood. These factors are often associated with the quality of the home environment, maternal health and the child's relationship with caregivers.

A previous study found high rates of antenatal depression in South Africa, with depression during pregnancy highly associated with antenatal alcohol use.[65]

Research further suggests that mothers with major depression from low income communities are less involved, less sensitive and more negative when interacting with their infants, affecting maternal-child rearing behaviours, impeding cognitive stimulation and directly affecting the maternal-infant bond.[66,67] Because children are less receptive to attachment after three years of age it is imperative that early bonding problems be identified within the first nine months of an infant's life, which may decrease the emergence of many later dysfunctions.

Findings from the current study confirm the association between developmental delay during infancy, on the performance scale measuring manipulation skill, speed and precision of work and maternal depression. The impact of socio-economic factors from infancy through to early childhood on developmental domains fortifies the idea that children develop in relation to their environment, not in isolation to it.[68]

Conclusion

Around 200 million children under the age of 5 in developing countries do not reach their potential.[49] Yet, only a small percentage of research addresses childhood development from impoverished backgrounds.[69] Previous key psychiatric interventions have attempted to use depression and HIV as the port of entry into a family, however this proved difficult, particularly within peri-urban areas with limited mental health services for diagnosis.[70]

With high rates of adverse social factors and alcohol abuse amongst impoverished communities, frontline primary health care staff should make specific efforts to identify high risk families especially among women attending antenatal clinics. Doing this is an essential step for ensuring that women at high-risk receive not only combined interventions for alcohol use, depression and other co-morbid psychiatric disorders associated with alcohol abuse but possibly preventing the birth of a child with FASD. Similarly, early recognition of children with FASD may significantly decrease secondary disabilities associated with Fetal Alcohol Syndrome. Indirectly this type of intervention would strengthen important factors within the micro environment, Firstly, that of the emotional state of the mother and her responsiveness to her child. Secondly, the social support she receives from others and thirdly, the protection offered to the child with particular reference to alcohol use and abuse.[56]

Caution is needed in using and generalising the study findings. The relatively homogenous racial composition of the sample does not reflect South Africa more broadly. Inclusion of only infants from predominately a rural area further limits the study's generalisability. The sample size was small, with limited power to detect differences between groups. The low response rate of Non-FASD children at 17-21 months and possible presence of subclinical effects of alcohol within this group might incur developmental bias. Finally, some limitations stem from the use of the GMDS tool, which tends to measure general ability in completing a given task, but may have low sensitivity for detecting minor developmental delays especially during infancy.[18,48]

Despite these limitations, the current study sheds light on early development of children with and without FASD in an impoverished community in South Africa. Furthermore, it

describes socio-economic factors, present in the community which appear to contribute to the nature and extent of developmental delay. Addressing developmental delay in peri-urban communities is complicated by the lack of specialists and competing demands on primary health care staff. Nevertheless, these findings highlight the importance of high-quality national psycho-educational and prevention programmes that are multidisciplinary and focused on increasing the ability of staff at primary health facilities to identify high-risk families and to provide preventive interventions, especially in antenatal clinics, as well as early intervention services.

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References

1. *Newton RW, Wraith JE. Investigation of developmental delay. Arch Dis Child 1995; 72(5):460-5.*
2. *Jones KL, Smith DW. Recognition of the Fetal Alcohol Syndrome in Early Infancy. Lancet 1973; (3):999-1001.*
3. *May PA, Brooke L, Gossage JP, Croxford J, Adnams C, Jones KL, et al. Epidemiology of Fetal Alcohol Syndrome in a South African Community in the Western Cape Province. American Journal of Public Health 2000; 90(12):1905-1912.*
4. *May PA, Gossage JP, Marais AS, Adnams CM, Hoyme HE, Jones KL. The epidemiology of fetal alcohol syndrome and partial FAS in a South African community. Drug Alcohol Depend 2007 ; 11(2-3):259-271.*
5. *Viljoen DL. Fetal Alcohol Syndrome-South Africa. Morbidity and Mortality Weekly Report July 18, 2003.*
6. *Urban M, Chersich MF, Fourie LA, Chetty C, Olivier L, Viljoen D. Fetal alcohol syndrome among grade 1 schoolchildren in Northern Cape Province: prevalence and risk factors. S Afr Med Journal 2008 ; 98(11):877-82.*
7. *Stratton K, Howe C, Battaglia F. Institute of Medicine. Fetal Alcohol Syndrome Diagnoses, Epidemiology, Prevention, and Treatment. Washington D.C: National Academy Press. 1996.*
8. *Mattson SN, Riley EP, Grambling L, Delis DC, Jones KL. Heavy prenatal alcohol exposure with or without physical features of fetal alcohol syndrome leads to IQ deficits. J Pediatr 1997; 131:718-721.*
9. *Streissguth AP, Barr HM, Sampson PD. Moderate prenatal alcohol exposure: Effects on child IQ and learning problems at age 7 ½ years. Alcohol Clin Exp Res 1990; 14:62-669.*
10. *Conry J. Neuropsychological deficits in fetal alcohol syndrome and fetal alcohol effects. Alcohol Clin Exp Res 1990 ; 14(5):650-655.*
11. *Carmichael Olson H, Feldman JJ, Streissguth AP, Sampson PD, Bookstein FD. Neuropsychological Deficits in Adolescents with Fetal Alcohol Syndrome: Clinical Findings. Alcohol: Clinical and Experimental Research 1998; 22(9):1998-2012.*
12. *Coles CD, Platzman KA, Raskind-Hood CL, Brown RT, Falek A. A comparison of children affected by prenatal alcohol exposure and attention deficit, hyperactive disorder. Alcohol Clin Exp Res 1997; 21:150-161.*
13. *Kodituwakku PW, Handmaker NS, Cutler SK, Weathersby EK, Handmaker SD. Specific impairments in self-regulation in children exposed to alcohol prenatally. Alcohol Clin Exp Res 1995; 19(6): 1558-1564.*
14. *Coles CD, Brown RT, Smith IE, Platman KA, Erickson S, Falek A. Effects of prenatal alcohol exposure at school age: I Physical and cognitive development. Neurotoxicol Teratol 1991; 13:357-367.*
15. *Kodituwakku PW, Kalberg W, May PA. The effects of prenatal alcohol exposure on executive functioning. Alcohol Res Health 2001; 25(3): 192-198.*
16. *Adnams C, Kodituwakku PW, Hay A, Molteno CD, Viljoen DL, May PA. Patterns of cognitive-motor development in children with fetal alcohol syndrome from a community in South Africa. Journal of Alcoholism: Clinical and Experimental Research 2001; 25(4):557-562.*
17. *Streissguth A, Barr H, Kogan J, Bookstein F. Understanding the Occurrence of Secondary Disabilities in Clients With Fetal Alcohol Syndrome (FAS) and Fetal Alcohol Effects (FAE): Final Report for Center for Disease Control & prevention. Seattle. University of Washington. 1996.*
18. *Emsley R. Focus on psychiatry in South Africa. British Journal of Psychiatry 2001; 178:382-386.*
19. *Stein DJ, Betancourt OA, Emsley RA, Jeenah Y, Mkize D, Pretorius J et al. Sub-specialties in psychiatry: Towards parity in mental health training and services. S Afr Med J 2009; 99 (1): 38-39.*
20. *Werner E, Simonian K, Bierman JM, French F. Cumulative effect of perinatal complications and deprived environment on physical and intellectual and social development of preschool children. Paediatrics 1967; 39:490-505.*
21. *Werner E, Bierman JM, French FE, Simonian K, Connor Q, Smith RS, Campbell M. Reproductive and environmental causalities: A report on the 10 year follow- up of children of Kauai pregnancy study. Paediatrics 1968; 42(10):13-127.*
22. *Wedge P, Prossor H. Born to Fail. Arrow Books. London. 1973.*
23. *Silva PA, Mcgee R, Thomas J, Williams S. A descriptive study of socio-economic status and child development in Dunedin fiver year olds. NZJ Ed Study 1985 ; 17 (1):21-32.*
24. *Bronman SH, Nichols PL, Kennedy WA. Preschool IQ: prenatal and early developmental correlates. John Wiley and Sons. 1975.*
25. *Neligan G, Prudham D, Steiner H. The formative year: birth, family and development in Newcastle. University Press. 1974.*
26. *Martin C, Gaffan EA. Effects of early maternal depression on patterns of infant-mother attachment: a meta-analytic investigation. Journal of Child Psychology Psychiatry2000; 41: 737-747.*
27. *Atkinson L, Paglia A, Coolbear J, Niccols A, Parker KCH, Guger S. Attachment security: a meta-analysis of maternal mental health correlates. Clin Psychol Rev 2000; 20: 1019-1040.*
28. *Campbell SB, Brownell CA, Hungerford A, Speiker SJ, Mohan R, Blessing JS. The course of maternal depressive symptoms and maternal sensitivity as predictors of attachment security at 36 months. Dev Psychopathol 2004; 16: 231-252.*
29. *Patel, V, Rodrigues M, De Souza N. Gender, poverty and postnatal depression: a study of mothers in Goa, India. Am J Psychiatry 2002; 159: 43-47.*
30. *Burd L, Cotsonas-Hassler TM, Martsolf JT, Kerbeshian J. Recognition and management of fetal alcohol syndrome. Neurotoxicol Teratol 2003 ; 25(6):681-688.*
31. *Hoyme HE, May PA, Kalberg WO, Kodituwakku P, Gossage JP, Trujillo PM et al. A practical clinical approach to diagnosis of fetal alcohol spectrum disorders: clarification of the 1996 institute of medicine criteria. Pediatrics 2005 ; 115(1):39-47.*
32. *May PA, Gossage JP, Brooke LE, Snell CL, Marais AS, Hendricks et al. Maternal risk factors for fetal alcohol syndrome in the Western Cape*

province of South Africa: a population-based study. Am J Public Health 2005 ; 95(7):1190-1199.
33. Griffiths R. The Abilities of Young Children. London: University of London Press. 1954.
34. Griffiths R. The abilities of young children. Amersham, ARICD. 1984.
35. Allan M.M. A comparison of the performance of normal preschool South African and British children on the Griffiths Scales of Mental Development; Unpublished Master's thesis, University of Port Elizabeth. South Africa 1988.
36. Allan MM. The performance of normal preschool South African children on the Griffiths Scales of Mental Development: A Comparative Study. Unpublished Doctoral thesis, University of Port Elizabeth, South Africa. 1992.
37. Bhamjee RA. A comparison of the performance of normal British and South African children on the Griffiths Mental Developmental Scales. Unpublished thesis, University of Port Elizabeth. South Africa. 1991.
38. Heimes L. The comparison of the JSAIS and the Griffiths Developmental Scale scores of 3-5 year old boys and girls. Unpublished Master's thesis, University of Port Elizabeth, South Africa. 1983.
39. Kotras H. Exploring the developmental profiles of black South African HIV+ infants using the revised Griffiths Mental Development Scales. Unpublished Master's thesis, University of Port Elizabeth. South Africa. 2001.
40. Lombard M. The SETT and the Griffiths Mental Developmental Scales. A correlative study. Unpublished Master's thesis, University of Port Elizabeth. South Africa. 1989.
41. Luiz DM. A child with a hearing loss: A longitudinal study in: Luiz DM, (Ed). Griffith Scales of Mental Developmental, South African studies (Research Papers No. C25) Port Elizabeth, University of Port Elizabeth. 1988a:44-51.
42. Luiz DM. A battered child: A follow up study. In DM Luiz (Ed), Griffiths Scales of Mental Development, South African studies (Research Papers No. C25) Port Elizabeth, University of Port Elizabeth. 1988b:52-58.
43. Luiz DM. A comparative study of two scales of language development, The Reynell and the Griffiths. In Luiz DM (Ed), Griffith Scales of Mental Development, South African studies (Research Papers No C25) Port Elizabeth, University of Port Elizabeth. 1988c:16-20.
44. Luiz DM. Children of South Africa: In search of a developmental profile: Inaugural and Emeritus Address. Port Elizabeth. University of Port Elizabeth. 1994.
45. Mothule VB. The Aptitude Test for Beginners and the Griffiths Mental Developmental Scales. An investigation into the assessment of the cognitive abilities of grade 1 children. Unpublished Master's thesis. Medical University of South Africa. Pretoria. 1990.
46. Sweeney K. Cluster analysis of the Griffiths profiles of a white South African clinical population Unpublished Master's thesis. University of Port Elizabeth. South Africa. 1994.
47. Tukulu AN. The Denver II Scale and the Griffiths Mental Developmental Scales: A correlational study. Unpublished master's thesis. University of Port Elizabeth. South Africa. 1996.
48. Cockcroft K, Amod Z, Soellaart B. Level of maternal education and performance of Black, South African infants on the 1996 Griffiths Mental Development Scales. Afr J Psychiatry 2008 ; 11(1):44-50.
49. Grantham Mcgregor S, Cheung YB, Cueto S, Glewwe P, Richter L, Strupp B. Developmental potential in the first 5 years for children in developing countries. The Lancet 2006; 369:60-70.
50. Luiz D, Barnard A, Knosen N, Kotras N, Horrocks S, McAlinden P, et al. GMDS-ER 2-8 Griffiths Mental Developmental Scales – Extended Revised: 2 to 8 years. 2006. Association for Research in Infant and Child Development (ARICD).
51. Viljoen D, Craig P, Hymbaugh K, Boyle C, Blount S. Fetal alcohol syndrome – South Africa 2001. MMWR 2003; 52(28):660-662.
52. Sobell S, Agarwal S, Annis H, Ayala-Velazquez H, Echeverria L, Leo GI et al. Cross-cultural evaluation of two drinking assessment instruments: alcohol follow -back and inventory of drinking situations. Subst Use Misuse 2001; 36:313-331.
53. Viljoen DL, Gossage JP, Brooke L, et al. Fetal alcohol syndrome epidemiology in a South African community: a second study of a very high prevalence area. J Stud Alcohol 2005; 66(5):593-604.
54. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961; 4:561-571.
55. Ward CL, Flisher AJ, Zissis C, Muller M Lombard C. Reliability of the Beck Depression Inventory and the Self Rating Anxiety Scale in a Sample of South African Adolescents. J Child and Adoles Mental Health 2003; 15(2):73-75.
56. Richter LM. The psychosocial factors in child health. Kibel MA & Wagstaff, eds Child Health For All: A manual for Southern Africa. Second Edition Cape Town: Oxford University Press, 1995:16-20.
57. Hurt H, Brodsky N, Betancourt L, Braitman L, Malmud E, Gianneta J. Cocaine exposed children: Follow up through 30 months. Journal of Developmental and Behavioural Paediatrics 1995; 16:29-35.
58. Hurt H, Malmud E, Betancourt L, Braitman L, Brodsky N, Gianetta J. Children with in utero cocaine exposure do not differ from control subjects in intelligence testing. Archives of Paediatrics and Adolescent Medicine 1997; 151:1237-1241.
59. Johnson DE. Medical and developmental sequela of early childhood institutionalisation in Eastern European adoptees. In Berk, L. Child Development .6th Edition, Boston: Allyn & Bacon. 2000.
60. Brooks-Gunn J, Klebanov PK, Duncan GJ. Ethnic differences in children's intelligence test scores: role of economic deprivation, home environment, and maternal characteristics. Child Dev 1996 Apr; 67(2):396-408.
61. Petterson SM, Albers AB. Effects of poverty and maternal depression on early child development. Child Dev 2001 ; 72(6):1794-813.
62. Skeels HM. Adult status of children with contrasting early life experiences. A follow-up study. Monogr Soc Res Child Dev 1966; 31(3):1-56.
63. Sirin SR. Socioeconomic status and academic achievement: A meta-analytic review of research. Rev Educ Res 2005; 75(3):417-453.
64. Goyen TA, Lui K. Longitudinal motor development of "apparently normal high-risk infants at 18 months, 3 and 5 years. Early Hum Dev 2002 Dec; 70(1-2):103-15.
65. Vythilingum B. Depression, Stress and Substance Use in South African pregnant women. Poster session presented at the International Anxiety Disorder Symposium, Stellenbosch Cape Town South Africa. May 2010.
66. Engle PL, Black MM, Behrman JR, Cabral de Mello M, Gertler PJ, Kapiriri L et al. Child development in developing countries 3: Strategies to avoid the loss of developmental potential in more than 200 million children in the developing world. The Lancet. 2007; 369:229-242.
67. Walker SP, Wachs TD, Meeks Gardner J, Lozoff B, Wasserman GA, Pollott E, Carter JA et al. Child development in developing countries 2: Child development: risk factors for adverse outcomes in developing countries. Lancet 2007; 369:145-157.
68. Bronfenbremmer U. The Ecology of Human Development: Experiments by Nature and Design. Harvard University Press. 1979.
69. Tomlinson M. Culture and infancy: a critical examination. S Afr J Child Adoles Mental Health 2003; 15(1):45-48.
70. Tomlinson M. Family-centred HIV interventions: lessons from the field of parental depression. Journal of the International AIDS Society 2010; 13(2):S9.

ANNEXURE 2 – STUDY 7

Davies L-A, Cockcroft K, Olinger L, Chersich M, **Urban M**, Chetty-Makkan CM, Turnbull OH, Olivier L, Viljoen D. Alcohol exposure during pregnancy alters childhood developmental trajectories in a rural South African community. *Acta Paediatrica*, epub ahead of print, July 2017 DOI:10.1111/apa.13978

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REGULAR ARTICLE

Alcohol exposure during pregnancy altered childhood developmental trajectories in a rural South African community

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ABSTRACT

Aim: This study examined the effects of prenatal alcohol exposure on childhood development trajectories in a rural South African community between 2003 and 2008.

Methods: We assessed 121 children at 7–12 months (year one) and 5–6 years (year five) using the Griffiths Mental Developmental Scales – Extended Revised, which measures sensorimotor, cognitive and social development, with lower scores indicating developmental delay. We also interviewed their mothers or caregivers. Three groups were identified: 29 with foetal alcohol syndrome (FAS) or partial FAS (pFAS), 57 more who had been exposed to alcohol and 35 controls who had not.

Results: The scale's total score was higher in the controls than in the FAS/pFAS group at year one and year five and in the alcohol-exposed group at year five. Many groups' trajectories declined when compared with global norms, but the trajectories in the FAS/pFAS and the alcohol-exposed groups declined more than the controls for eye-hand and performance and total score. Earlier pregnancy recognition in the FAS/pFAS group correlated strongly ($r = -0.77$) with higher GQ in year five.

Conclusion: FAS/pFAS and prenatal alcohol exposure affected the Griffiths scores more than the control group. Efforts are needed to detect pregnancy early and reduce alcohol exposure.

INTRODUCTION

Prenatal alcohol exposure can cause devastating structural and functional abnormalities in the developing foetus, which manifests as cognitive and developmental deficits in children. Heavy prenatal alcohol exposure, especially binge drinking (1,2), is classically associated with foetal alcohol spectrum disorder (FASD), which encompasses a continuum of physical, cognitive and behavioural outcomes (2–4). These outcomes include lowered intellectual ability (1,4,5) and deficits in language (4,6), motor skills (7,8) attention (9) and behaviour (10).

Functional deficits in areas of higher-order cognition, such as executive functions, are commonly described in children prenatally exposed to alcohol and these include planning, organising, sequencing, problem solving (11,12) and working memory (8,13). These cognitive deficits reflect the fundamentals of learning and may even occur in the absence of facial features associated with foetal alcohol syndrome (FAS) or partial foetal alcohol syndrome (pFAS). In this situation, the link between cause and effect makes it difficult to identify non-syndromic alcohol-exposed children (2,4). While the amount and timing of alcohol intake is

Abbreviations
FASD, Foetal alcohol spectrum disorders; FAS, Foetal alcohol syndrome; GMDS-ER, Griffiths Mental Developmental Scales – Extended Revised; GQ, General quotient; pFAS, Partial foetal alcohol syndrome.

Key notes
- We examined the effects of prenatal alcohol exposure on childhood development trajectories in a rural South African community between 2003 and 2008 using the Griffiths Mental Developmental Scales – Extended Revised.
- Our prospective study of 121 children showed heavy maternal alcohol consumption affected overall development at 7–12 months, with lower levels of alcohol affecting higher-order abilities at 5–6 years.
- Efforts are needed to detect pregnancy early and reduce alcohol exposure.

an important determinant of FASD outcomes, there is evidence that individual susceptibility and other risk factors play a big role.

Within the context of early childhood development, it is clear that a complex interplay of factors, in addition to alcohol exposure, is critical determinant of child outcome. Importantly, negative consequences of the cumulative effects of socio-economic deprivation on development may accrue overtime (14). Other factors include prenatal and post-natal nutrition, birth weight, maternal age, maternal body mass index, parity, maternal stress and depression, a family history of neurodevelopmental disorders, parenting styles, neglect and general lack of stimulation (15–17).

While considerable research exists describing the developmental deficits of children exposed to heavy prenatal alcohol use, as described above, there is surprisingly little data available on early developmental profiles and trajectories of children with varying degrees of prenatal alcohol exposure in low-income and middle-income countries. The study provided a unique opportunity to assess early developmental domains in a poorly-resourced population that we knew had a high prevalence of FASD. This study aimed to compare the developmental trajectories of children with FAS/pFAS, children who were exposed to alcohol during pregnancy but did not meet the criteria for FAS/pFAS and controls whose mothers did not drink during pregnancy. Our special focus was on the alcohol-exposed group. The study also assesses the role of other factors associated with poor developmental outcome.

METHODS

Participants were recruited, between 2003 and 2008, from a sheep farming area in the Upper Karoo region of the Northern Cape, once the largest railway junction in South Africa. When railway operations were significantly reduced due to route restructuring, the high unemployment and concomitant socio-economic deprivation that occurred as a result contributed to the already high levels of alcohol abuse in the area. This area of South Africa is well known to researchers in the field of FASD, as it has one of the highest reported incidences of FASD in the world and this has been described in a school-entry population (3).

Data for this study were drawn from a larger FASD prevention study in the Northern Cape (18). This analysis, followed the study children up to 5 years of age, extending previous data when the children were between 7–12 months of age and 17–21 months of age (18,19). Written informed consent was obtained from the mothers' at all three points. The mothers of 500 children born in the local hospital between 2002 and 2003 were invited to participate. Of those children born, 394 were assessed at 7–12 months of age, year one, and 135 returned when they were between five and 6 years of age, year five (Fig. 1). Differences in the sample size between years one and five were mostly due to resource constraints, which precluded the selection of more control participants, and this meant that 247 were not invited back at year five. The loss of seven participants because of death or mobility issues and 19 with missing data further reduced the sample size (Fig. 1). At years one and five, the participants were evaluated at a local community centre, by two paediatricians with training in medical genetics, for dysmorphic features and neurological signs associated with FAS or pFAS (2).

A semi-structured questionnaire, piloted within the local population, was administered to biological mothers at year one, by a trained interviewer or neuropsychometrist (20). Some mothers were interviewed at a later assessment between 17–21 months of age. Where the mothers died or were untraceable, shorter proxy interviews were conducted with the primary caregiver. The tool elicited maternal demographic and lifestyle information, such as the occurrence and amount of maternal drinking and smoking. A history of maternal alcohol consumption in pregnancy was obtained through a maternal interview using a timeline follow-back method (2). Referrals were made to specialist services where necessary, and feedback on the child's development was provided to families. The study was approved by the University of the Witwatersrand Ethics Committee for Research on Human Subjects (numbers M01/11/20; M09/02/22).

Inclusion in this analysis depended on the child having completed both clinical and neurodevelopmental assessments at years one and five and the mother having completed a maternal interview. A final diagnosis of FAS and pFAS was made at the year five assessment, based on the revised Institute of Medicine criteria (2). In brief, a diagnosis of FAS required the presence of at least two of three characteristic facial features, namely short palpebral fissures (<10th percentile), thin vermilion border and, or, smooth philtrum of the lip, as well as growth deficiency – based on ≤10th percentile for height and weight, or head circumference - and evidence of central nervous system abnormalities. A pFAS diagnosis required at least two of three facial features listed above as well as either: growth deficiency, evidence of central nervous system abnormalities and, or, unexplained cognitive/behavioural abnormalities. Although the clinical diagnoses of both FAS and pFAS are considered distinctive in the absence of confirmed maternal alcohol consumption during pregnancy (2), our criteria required a history of alcohol use in pregnancy.

The alcohol-exposed group comprised children who were non-symptomatic for FAS/pFAS features, but whose mothers confirmed drinking prior to the recognition of their pregnancy or at any point during their pregnancy. The controls consisted of participants with no evidence of clinical FAS/pFAS features and no reported alcohol exposure during pregnancy. Children were assigned to one of the three groups (Fig. 1): 29 (24%) in the FAS/pFAS group, 57 (47%) in the alcohol-exposed group and 35 (29%) in the controls group. Of the 29 children diagnosed with FAS/pFAS at year five, four (14%) had been classified as alcohol-exposed at year one and just one changed from a FAS/pFAS diagnosis at year one to a non-exposed case at year five.

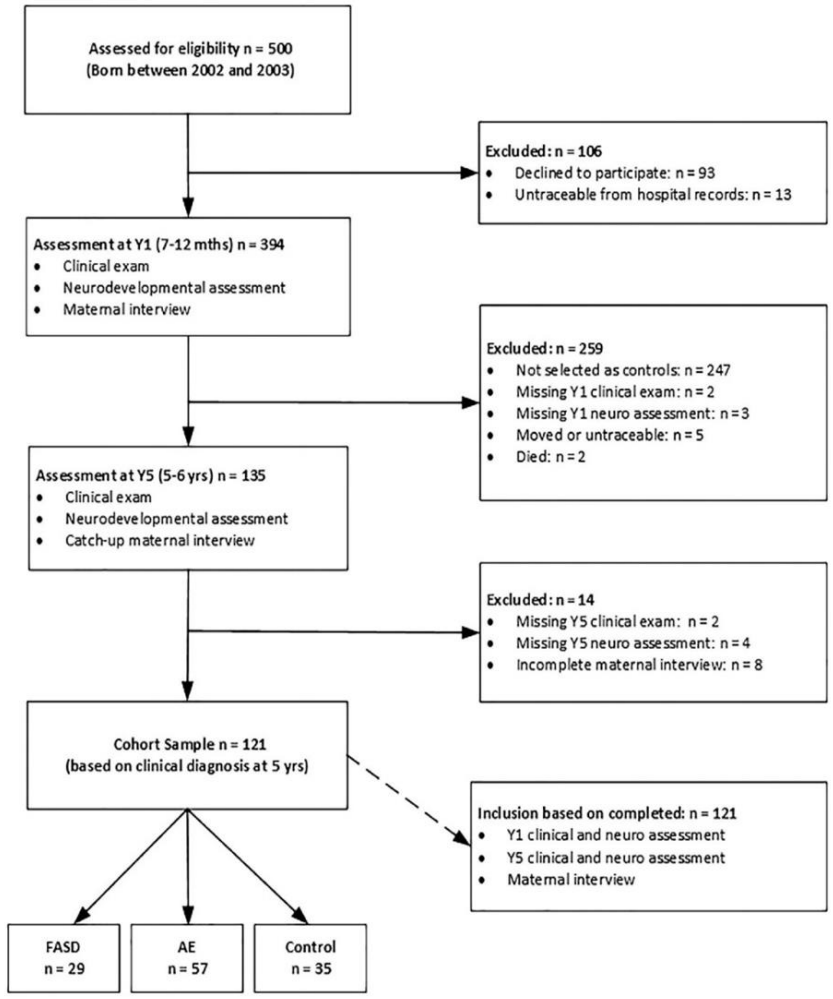

Figure 1 Recruitment and attrition of participants in study.

Neurodevelopmental study measures

The Griffiths Mental Developmental Scales – Extended Revised (GMDS-ER) assesses three key developmental domains over six scales from infancy to middle childhood, namely: sensorimotor development, which focuses on gross and fine motor coordination, as measured by the locomotor and eye-hand scales; cognitive development associated with higher-order abilities such as manipulation, problem solving and reasoning, measured by the language, performance and practical reasoning scales; and social development, measured by the personal-social scale (21). The general quotient (GQ), which determines overall development, is a composite of these six subscale scores. Means range between 99.87 and 100.46, with standard deviation scores

from 0.58 to 17.43 (21). A standard score of 100 would place the child's performance within the average range whereas a score below 70 (<2 standard deviations) would indicate a significant degree of developmental delay (22). Age equivalents or mental age, based on tables from the analyses manual, were used in conjunction with the chronological age and plotted as developmental trajectories for the total GQ and each subscale. The only exception was the practical reasoning scale, as this was only measured at year five. Age-appropriate versions of the GMDS-ER measured developmental functioning at years one and five, with prematurity corrected at year one. The GMDS-ER was developed in the United Kingdom, and although it does not provide normal measures for South African children, it has been extensively used to assess the development of local children in the country (22,23). Existing Afrikaans and Xhosa translations were used. The developmental outcomes of the GMDS-ER subscales were not used for the diagnosis of FAS/pFAS. Although a new third edition of the tool has since been developed, previous versions of the tool assess similar constructs of childhood development.

Statistical analyses

Analyses were carried out using Intercooled Stata 12.1 (Stata Corporation, College Station, TX, USA). Continuous data across the three groups were analysed using the Kruskal–Wallis analysis of variance for non-normal variables and one way ANOVA for normally-distributed variables. Where significant differences were observed across the groups, further post hoc analyses were carried out using Mann–Whitney U and Student's *t*-tests, to compare differences between the controls and alcohol-exposed groups and between controls and FAS/pFAS groups. Frequency distributions and chi-square tests were used for analysing the categorical data. Pearson's correlation coefficients identified univariate linear associations between the normally-distributed variables, birth weight and the GMDS-ER subscale scores, as well as the associations between the year one and year five GMDS-ER subscale scores for the three groups. A series of Spearman's correlation coefficients (r) were used to detect univariate associations between all other non-normal variables and the GMDS-ER subscale scores, for outcomes at both year one and year five for each group. Finally, multiple linear regressions were used to identify factors associated with total GQ scores at years one and five. The model selection was based on backward elimination of non-significant factors ($p > 0.05$), the clinical significance of factors based on existing evidence and the relative quality of the model as measured by the Akaike Information Criterion. Alcohol use during pregnancy was excluded from the multivariate regression model, as it is a proximal variable on the causal chain between FAS/pFAS and neurological outcomes.

RESULTS

The sample characteristics, by study group are shown in Table 1. As expected, infants diagnosed with FAS/pFAS were smaller in terms of length and head circumference at birth and much more likely to be premature: 31% versus 3% of controls and 12% of alcohol-exposed subjects. They were also much more likely to be underweight at birth, defined as ≤2.5 kg: 64%, versus 18% of controls and 24% of alcohol-exposed subjects. Significant anthropometric differences continued between the groups at years one and five ($p < 0.001$). For many of the indices measured, including alcohol units per week during pregnancy, the levels in the alcohol-exposed group were midway between those of the FAS/pFAS subjects and the controls. For example, 54% of the mothers of alcohol-exposed children smoked during pregnancy (30/56), about equidistant from the levels in the controls (17%, 6/35) and FAS/pFAS women (76%, 22/29).

Group differences

In terms of overall development, the total GQ means shown in Table 2 indicated no significant differences between the control and alcohol-exposed groups at year one, but notable differences by year five ($p = 0.026$). The subscales which contributed to the decline at year five included poor eye-hand coordination, performance and practical reasoning. The mean scores were numerically lower than the controls for the FAS/pFAS group over all domains at both time points, when compared to the alcohol-exposed and control groups.

Effects of prenatal alcohol exposure on developmental trajectories

Within the FAS/pFAS group, language, eye-hand coordination and performance deteriorated the most overtime and at approximately the same rate (Fig. 2). While locomotor abilities improved by year five, personal-social skills remained fairly constant. Similar patterns of development were observed in the alcohol-exposed group, with notable declines observed in both the performance and language subscales. A large disparity was noted between the scores at year five in locomotor and personal-social, which both improved steadily, when compared to the remaining subscales, which all deteriorated. Steady trajectory declines were also evident overtime in the control group with regard to language, eye-hand coordination and performance skills.

To account for anticipated delay among the FAS/pFAS group, mental age equivalent scores were plotted for all groups over the total GQ. The GQ trajectories increased steadily overtime, with the control and alcohol-exposed groups following a similar pattern of development. The FAS/pFAS group showed a trajectory than ran below and parallel to both the control and the alcohol-exposed groups. This parallel trajectory suggests that, while development was delayed in onset, it generally occurred at the same rate in the three groups. When chronological and mental age performances were compared, slower developmental rates become evident for all groups.

Effects of socio-demographic variables on development

Correlations were sought between the GMDS-ER subscale and GQ scores and the following variables: maternal

Table 1 Infant, maternal, pregnancy and lifestyle variables based on FASD group allocation (N = 121)

	Variable group	Category, n/N (%)	Control (35/121)	Alc exposed (57/121)	FAS/PFAS (29/121)	p
Infant	Gender	Female	22/35 (63)	31/57 (54)	18/29 (62)	.663
	Ethnicity	Black	7/35 (20)	10/57 (18)	7/29 (24)	.769
		Mixed ethnicity	28/35 (80)	47/57 (82)	22/29 (76)	
	Anthropometry†	Prematurity	1/35 (3)	7/57 (12)	9/29 (31)	**.005**
		Less than 2.5 kg	6/33 (18)	13/55 (24)	16/25 (64)	**<.001**
		Birth length mean cm (sd), n	49.8 (3.6), 31	49.2 (4.1), 54	45.7 (5.7), 23	**.002**
		Birth weight mean kg (sd), n	2.97 (0.4), 34	2.77 (0.6), 54	2.26 (0.5), 25	**<.001**
		Birth OFC mean cm (sd), n	34.8 (1.9), 32	33.9 (2.4), 54	32.2 (2.7), 25	**<.001**
Year 1		Length mean cm (sd), n	70.1 (3.0), 35	68.7 (4.1), 57	64.3 (3.7), 29	**<.001**
		Weight mean kg (sd),n	8.4 (1.1), 35	7.6 (1.5), 57	5.9 (0.9), 29	
		OFC mean cm (sd), n	45.2 (1.4), 35	44.5 (1.8), 57	42.5 (1.3), 29	
Year 5		Length mean cm (sd)	105.6 (4.4), 35	101.4 (6.4), 57	95.3 (5.7), 29	**<.001**
		Weight mean kg (sd)	17.0 (2.1), 35	15.8 (2.4), 57	12.8 (1.6), 29	
		OFC mean cm (sd)	50.9 (1.4), 35	50.1 (1.6), 57	48.1 (1.4), 29	
Maternal	Maternal age†	Mean yrs (sd), n	25.6 (6.5), 33	26.8 (6.2), 56	31.1 (6.6), 28	**.002**
	Marital status†	Married/engaged	8/31 (26)	15/55 (27)	5/29 (17)	**.040**
		Divorced/widowed	1/31 (3)	3/55 (6)	0/29 (0)	
		Unmarried, living with partner	5/31 (16)	14/55 (26)	16/29 (55)	
		Single	17/31 (55)	23/55 (42)	8/29 (28)	
	Education level†	No formal schooling	1/32 (3)	2/54 (4)	6/28 (21)	**<.001**
		Incomplete primary	2/31 (6)	9/54 (17)	9/28 (32)	
		Complete primary	3/31 (10)	10/54 (18)	4/28 (14)	
		Incomplete secondary	11/31 (36)	25/54 (46)	9/28 (32)	
		Complete secondary	14/31 (45)	8/54 (15)	0/28 (0)	
	Maternal occupation†	Full time	10/31 (32)	10/54 (19)	1/29 (3)	*.055*
		Part time	5/31 (16)	11/54 (20)	5/29 (17)	
		Unemployed	16/31 (52)	33/54 (61)	23/29 (79)	
	Parity†	Mean # of children (sd), n	2.1 (1.3), 34	2.7 (1.6), 57	3.2 (1.5), 29	*.007*
Pregnancy & lifestyle		Death of a child	4/34 (12)	9/57 (16)	11/29 (38)	.019
	Month pregnancy discovered†	Mean (sd), n	3.0 (1.5), 24	3.8 (1.4), 34	4.2 (1.9), 9	*.070*
	Smoking during pregnancy†	n/N (%)	6/35 (17)	30/56 (54)	22/29 (76)	**<.001**
	Alcohol units/week before pregnancy†	Median (IQR), n	0 (0), 35	13 (6-21),48	31 (18-61), 24	**<.001**

p-values <0.05 are bolded and those 0.05–0.1 in italics.
FASD=Fetal alcohol spectrum disorder; Alc exposed=Alcohol exposed; FAS=Fetal alcohol syndrome; PFAS=Partial fetal alcohol syndrome; IQR=Inter-quartile range; OFC=Occipital head circumference.
†Some data are missing.

educational level, marital status, occupation, parity, gestational month of pregnancy recognition, duration of breastfeeding, reported level of pre-pregnancy alcohol consumption, infant gender, ethnicity, the presence of prematurity, birth weight, length and head circumference. The only strong correlation that was detected was between gestational month of pregnancy recognition and neurodevelopmental outcome at year five in the FAS/pFAS group. This was true for GQ ($r = -0.77$), and was consistent across all domains, except for practical reasoning. A similar correlation was not found for the alcohol-exposed group.

Several other statistically significant, but weaker, correlations were also found for GQ as significance levels did not reach ≤0.5 for any other variable. In the control group, higher GQ at year five correlated with mothers being married, rather than cohabiting or single ($r = -0.48$), and with being Black African compared with mixed ethnicity ($r = 0.36$). For the alcohol-exposed group, higher GQ at year one, but not year five, correlated negatively with maternal parity ($r = -0.42$) and age ($r = -0.34$). In the FAS/pFAS group, a similar correlation was found for parity ($r = -0.37$), but not age ($r = -0.04$). Lastly, and only in the alcohol-exposed group, the year one GQ correlated with infant head circumference ($r = 0.27$), and the year five GQ correlated with the reported level of alcohol consumption ($r = -0.32$). Maternal educational level had no detectable effect.

Multiple regression analysis examined factors associated with total GQ scores at year one and year five, in multivariate models that included the study group. The above analyses identify associations separately for each study group. Due to missing data, the gestational month at pregnancy recognition variable could not be included in this analysis. In the multivariate model for year one, there

Table 2 Differences in mean GMDS subscales at Year 1 and Year 5 between study groups

GMDS subscales	Assessment	Control (A) (n = 35) Mean	Alc expo(B) (n = 57) Mean	FAS/PFAS (C) (n = 29) Mean	(A vs. B) p	(A vs. C) p
Locomotor	Year 1	97.3	98.0	88.9	.833	**.034**
	Year 5	107.6	109.5	97.4	.623	**.035**
Personal-social	Year 1	109.0	108.9	103.1	.974	.198
	Year 5	116.8	113.4	101.5	.357	**.001**
Language	Year 1	110.7	111.5	102.8	.744	**.015**
	Year 5	76.9	72.3	70.5	.159	.133
Eye-hand coordination	Year 1	100.6	100.1	94.4	.870	.135
	Year 5	88.3	80.3	68.5	**.033**	**<.001**
Performance	Year 1	97.9	95.7	91.5	.527	*.085*
	Year 5	79.9	69.0	63.3	**.002**	**.001**
Practical reasoning†	Year 5	90.1	81	73.2	**.010**	**<.001**
Total general quotient (GQ)	Year 1	103.2	102.8	95.9	.891	**.028**
	Year 5	93.2	87.3	78.8	**.026**	**< .001**

P-values <0.05 are bolded and those 0.05–0.1 in italics.
Year 1 = 7–12 months; Year 5 = 5–6 years; GMDS=Griffiths mental developmental scales; Alc Expo= Alcohol exposed; FAS=Fetal alcohol syndrome; PFAS=Partial fetal alcohol syndrome.
†Practical Reasoning subscale only included Year 5 assessment.

were significant associations with birth length at 0.73, with a 95% confidence interval (95% CI) of 0.24 to 1.22 (p = 0.001) and maternal parity (−3.04, 95% CI −4.59 to −1.50, p < 0.001). At year five, the association with birth length remained similar (0.80, 95% CI 0.28 to 1.33; p = 0.003) and there was an association with maternal age (0.53, 95% CI 0.12 to 0.93, p = 0.01). There was also an association with two of the study groups: alcohol-exposed −5.71, 95% CI −11.28 to −0.14 (p = 0.05) FAS/pFAS −12.06, 95% CI −20.04 to −4.07 (p = 0.003).

DISCUSSION

This prospective study compared the developmental trajectories from year one to year five for prenatally alcohol-exposed children without syndromic features to those of children with FAS/pFAS and to unexposed controls, in a poorly-resourced rural community in South Africa. The differences between the groups at year five, when the children were 5–6 years, were considerably larger than those reported in the same cohort when children were younger at 7–12 months and 17–21 months of age (19). As expected, infants diagnosed with FAS/pFAS performed worse at both year one and year five over most developmental domains when compared to other groups and struggled most with the higher-order cognitive tasks associated with manipulation and regulation. This difficulty with higher cognitive functions, which becomes even more apparent with age, has been well described with FAS (7,8,11,13,19).

The alcohol-exposed group fell between the control group and the FAS/pFAS groups in terms of alcohol consumption, but also in many other maternal and infant parameters. From a cognitive viewpoint, their GMDS-ER scores were similar at year one to the control group. However, by year five, they scored lower than the control group on the eye-hand coordination, performance and practical reasoning subscales and for the GQ as a whole. The lower GQ score at year five remained significant on multivariate analysis. The intermediate developmental status of the alcohol-exposed group, as well as the correlation of year five GQ with the level of alcohol intake in this group alone, was probably consistent with a dose-related effect of ethanol exposure on brain structure and function (24). This less severe exposure would have caused subtler or more region-specific effects, with the related adverse neurodevelopmental outcomes only becoming apparent later in childhood. Equally, it was consistent with the notion that as cognitive demands increase, those with even moderate levels of prenatal alcohol exposure find these demands more challenging (7,9,25).

Most children in the sample, regardless of their study group, experienced some delay in important areas of development. In all groups, the total GQ, as well as the subscales for language, eye-hand coordination and performance, declined between years one and five. This suggests that factors other than prenatal alcohol exposure affected child development in this setting. Many of the children in this study, including the controls, were exposed to other adverse life circumstances. For example, most of the mothers in all groups were unemployed and had not completed secondary education, many had experienced the death of a child and a relatively high proportion of infants in all groups had a low birth weight (18). It is known that neurodevelopment throughout childhood is strongly associated with socio-economic status, with children from low socio-economic status far more likely to falter compared to their wealthier counterparts (26). May et al.(24) showed that even in a South African setting with high exposure to prenatal alcohol, exposure to other poverty-

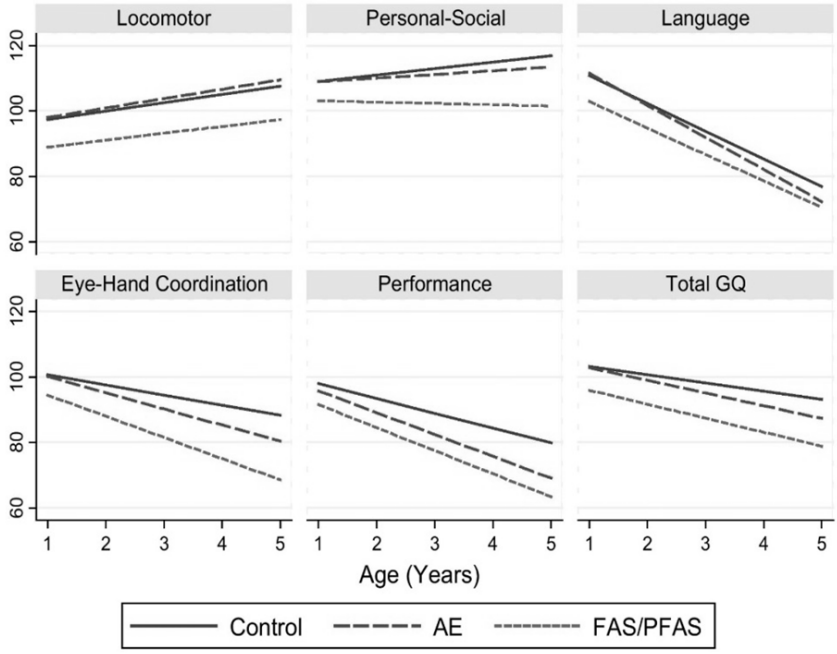

Figure 2 Trajectories of developmental abilities, comparing children with FAS/pFAS, alcohol exposure and a control group.

related factors appeared to outweigh the effect of prenatal alcohol exposure. These other important factors include both biological variables, such as nutrition and growth stunting, and psychological variables such as limited child stimulation, exposure to violence and maternal depression (26). To complicate the matter, where socio-economic status is kept optimal, adoption studies have showed serious damage of the exposed children in later childhood (27).

The greater drop off in GQ, eye-hand coordination and performance for both alcohol-exposed groups compared to the control group may, therefore, either represent the effect of ethanol exposure and of other prenatal and post-natal factors, or very likely a combination of all these. Overall, our findings confirmed the importance of addressing both maternal alcohol use and the immediate environment of at-risk women and children. Examples of interventions include FASD prevention strategies, optimising antenatal care, improving child nutrition, preschool services in poorly-resourced communities, parent training to provide more stimulated home environments and early developmental interventions.

It should be noted that the median maternal pre-pregnancy alcohol use was very high in the FAS/pFAS group and was relatively high even in the alcohol-exposed group. Late pregnancy recognition in the FAS/pFAS group was strongly correlated with lower GQ and poorer developmental functioning over higher cognitive domains at year five. The most likely explanation is that late recognition prolonged the period of foetal exposure to alcohol.

At year one, infants with reduced lengths at birth and higher maternal parity presented with delayed developmental trajectories. Previous studies reported how early stunting, at least partly attributable to prenatal nutritional deficiency, was associated with less schooling, poor test performances and low earnings in adulthood (14–17,28).

While we did not detect an association between ethnicity and alcohol exposure, we found a difference in neurodevelopmental outcomes between the control children of Black African and mixed ancestry. The reason for this is uncertain, but may have indicated differences in unreported drinking or in other environmental or parenting-related factors. It warrants further investigation.

Study limitations

Due to the limited size and the high-risk nature of the sample, caution should be used in extending these findings

to other populations. Further limitations stem from use of the GMDS-ER tool, which tends to measure general ability, but is less able to detect subtle or specific delays, especially during infancy (7). Furthermore, although this tool has been extensively used in research studies, direct comparisons between different versions of the GMDS developmental ranges are prone to misinterpretation due to differing means and standard deviations of the instrument (29). The use of mental age equivalents aimed to mitigate these limitations. It should be noted that the neurodevelopmental evaluation of alcohol effects in this study was limited to typically developing abilities at 5 years of age. It is possible that later effects on development should be investigated at an older age using other psychometric instruments and evaluations of behaviour.

Maternal alcohol histories are known to be sensitive and therefore potentially susceptible to bias, although there is considerable evidence that retrospective self-reports are more valid, or at least detect more alcohol use, than reports given during pregnancy (30).

CONCLUSION

All levels of prenatal alcohol exposure in this study influenced higher-order cognitive abilities in children at 5 years of age. While participants diagnosed with FAS/pFAS were often developmentally different to the controls at year one, larger differences became evident with age. In contrast, alcohol-exposed children that did not meet the FAS/pFAS criteria were developmentally similar to the controls at year one, but by year five they demonstrated significantly lower functioning in the eye-hand, performance and practical reasoning domains. In addition, their GQ was considerably lower at year five, including in the multivariate analysis. The developmental trajectories of all children in the study is a matter for concern and suggests that preschool services and other measures to stimulate child development may have a particularly critical role in this and similar local environments.

In the FAS/pFAS group, strong correlations emerged between earlier maternal pregnancy recognition and higher overall functioning in the year five GQ scores, and this finding was most likely to have been mediated by reduced drinking during pregnancy. However, it does emphasise the need for effective methods of preconception screening for alcohol use among South African women, together with alcohol education and counselling for women of childbearing age and early pregnancy recognition,.

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CONFLICTS OF INTEREST

The authors declare that they have conflicts of interests.

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References

1. Bailey BN, Delaney-Black V, Covington CY, Ager J, Janisse J, Hannigan JH, et al. Prenatal exposure to binge drinking and cognitive and behavioral outcomes at age 7 years. *Am J Obstet Gynecol* 2004; 191: 1037–43.
2. Hoyme HE, May PA, Kalberg WO, Kodituwakku P, Gossage JP, Truijillo PM, et al. A practical clinical approach to diagnosis of fetal alcohol spectrum disorders: clarification of the 1996 institute of medicine criteria. *Pediatrics* 2005; 115: 39–47.
3. Urban M, Chersich MF, Fourie LA, Chetty C, Olivier L, Viljoen D. Fetal alcohol syndrome among grade 1 schoolchildren in Northern Cape Province: prevalence and risk factors. *S Afr Med J* 2008; 98: 877–82.
4. Mattson SN, Crocker N, Nguyen TT. Fetal alcohol spectrum disorders: neuropsychological and behavioral features. *Neuropsychol Rev* 2011; 21: 81–101.
5. Streissguth AP, Bookstein FL, Barr HM, Sampson PD, O'Malley K, Young JK. Risk factors for adverse life outcomes in fetal alcohol syndrome and fetal alcohol effects. *J Dev Behav Pediatr* 2004; 25: 228–38.
6. McGee CL, Bjorkquist OA, Riley EP, Mattson SN. Impaired language performance in young children with heavy prenatal alcohol exposure. *Neurotoxicol Teratol* 2009; 31: 71–5.
7. Adnams CM, Kodituwakku PW, Hay A, Molteno CD, Viljoen D, May PA. Patterns of cognitive-motor development in children with fetal alcohol syndrome from a community in South Africa. *Alcohol Clin Exp Res* 2001; 25: 557–62.
8. Kalberg WO, May PA, Blankenship J, Buckley D, Gossage JP, Adnams CM. A practical testing battery to measure neurobehavioral ability among children with FASD. *Int J Alcohol Drug Res* 2013; 26: 51–60.
9. Coles CD, Kable JA, Keen CL, Jones KL, Wertelecki W, Granovska IV, et al. Dose and timing of prenatal alcohol exposure and maternal nutritional supplements: developmental effects on 6-month-old infants. *Matern Child Health J* 2015; 19: 2605–14.
10. Nash K, Rovet J, Greenbaum R, Fantus E, Nulman I, Koren G. Identifying the behavioural phenotype in Fetal Alcohol Spectrum Disorder: sensitivity, specificity and screening potential. *Arch Womens Ment Health* 2006; 9: 181–6.
11. Mattson SN, Goodman AM, Caine C, Delis DC, Riley EP. Executive functioning in children with heavy prenatal alcohol exposure. *Alcohol Clin Exp Res* 1999; 23(Suppl 11): 1808–15.
12. Skogerbo A, Kesmodel US, Wimberley T, Stovring H, Bertrand J, Landro NI, et al. The effects of low to moderate alcohol consumption and binge drinking in early pregnancy on executive function in 5-year-old children. *BJOG* 2012; 119: 1201–10.
13. Mattson SN, Roesch SC, Fagerlund A, Autti-Rämö I, Jones KL, May PA, et al. Toward a neurobehavioral profile of fetal alcohol spectrum disorders. *Alcohol Clin Exp Res* 2010; 34: 1640–50.

14. Engle PL, Black MM, Behrman JR, Cabral de Mello M, Gertler PJ, Kapiriri L, et al. Strategies to avoid the loss of developmental potential in more than 200 million children in the developing world. *Lancet* 2007; 369: 229–42.
15. Baker-Henningham H, Powell C, Walker S, Grantham-McGregor S. Mothers of undernourished Jamaican children have poorer psychosocial functioning and this is associated with stimulation provided in the home. *Eur J Clin Nutr* 2003; 57: 786–92.
16. Bradley RH, Corwyn RF. Socioeconomic status and child development. *Annu Rev Psychol* 2002; 53: 371–99.
17. Carter RC, Jacobson JL, Molteno CD, Dodge NC, Meintjies EM, Jacobson SW. Fetal alcohol growth restriction and cognitive impairment. To be published in *Pediatrics*. [Preprint] 2016. Available at: https://www.ncbi.nlm.nih.gov/pubmed/?term=27401098.
18. Chersich MF, Urban M, Olivier L, Davies LA, Chetty C, Viljoen D. Universal prevention is associated with lower prevalence of fetal alcohol spectrum disorders in Northern Cape, South Africa: a multicentre before-after study. *Alcohol Alcohol* 2012; 47: 67–74.
19. Davies L, Dunn M, Chersich M, Urban M, Chetty C, Olivier L, et al. Developmental delay of infants and young children with and without fetal alcohol spectrum disorder in the Northern Cape Province. *Afr J Psychiatry* 2011; 14: 298–305.
20. Viljoen D, Croxford J, Gossage JP, Kodituwakku PW, May PA. Characteristics of mothers of children with fetal alcohol syndrome in the Western Cape Province of South Africa: a case control study. *J Stud Alcohol* 2002; 63: 6–17.
21. Griffiths R. *The abilities of babies*. London: The Test Agency, 1986.
22. Luiz DM, Foxcroft CD, Tukulu AN. The denver II scales and the griffiths scales of mental development: a correlational study. *J Child Adolesc Ment Health* 2004; 16: 77–81.
23. Cockcroft K, Amod Z, Soellaart B. Level of maternal education and performance of Black, South African infants on the 1996 Griffiths Mental Development Scales. *Afr J Psychiatry* 2008; 11: 44–50.
24. May PA, Tabachnick BG, Gossage JP, Kalberg WO, Marais AS, Robinson LK, et al. Maternal factors predicting cognitive and behavioural characteristics of children with fetal alcohol spectrum disorders. *J Dev Behav Pediatr* 2013; 34: 314–25.
25. Kodituwakku PW, Kodituwakku EL. From research to practice: an integrative framework for the development of interventions for children with fetal alcohol spectrum disorders. *Neuropsychol Rev* 2011; 21: 204–23.
26. Grantham-McGregor S. Early child development in developing countries. *Lancet* 2007; 10: 824.
27. Streissguth AP, Barr HM, Kogan J, Bookstein FL. Understanding the occurrence of secondary disabilities in clients with fetal alcohol syndrome (FAS) and fetal alcohol effect (FAE). University of Washington Fetal Alcohol and Drug Unit Final report. Centre for Disease control and Prevention; 1996.
28. Graham K, West P, Wells S. Evaluating theories of alcohol-related aggression using observations of young adults in bars. *Addiction* 2000; 95: 847–63.
29. Ivens J, Martin N. A common metric for the Griffiths Scales. *Arch Dis Child* 2002; 87: 109–10.
30. Poikolainen K, Leppänen K, Vuori E. Alcohol sales and fatal alcohol poisonings: a time-series analysis. *Addiction* 2002; 97: 1037–40.

REFERENCES

1. McGovern P, Zhang J, Tang J, et al. Fermented beverages of pre- and proto-historic China. *Proc Natl Acad Sci U S A*. 2004;101(51):17593-17598.

2. Vouillamoz J, McGovern P, Ergul A, et al. Genetic charaterization and relationships of traditional grape cultivars from Transcaucasia and Anatolia. *Plant Genet Resour*. 2006;4(2):144-158.

3. Gateley I. *Drink: A Cultural History of Alcohol*. New York: Penguin Group; 2008.

4. Abel E. The gin epidemic: much ado about what? *Alcohol Alcohol*. 2001;36(5):401-405. doi:https://doi.org/10.1093/alcalc/36.5.401.

5. Simatende P, Gadaga T, Nkambule S, Siwela M. Methods of preperation of Swazi traditional fermented foods. *J Ethn Foods*. 2015;2(3):119-125.

6. World Health Organization. Guidelines for the identification and management of substance use and substance use disorders in pregnancy. *Guidel Identif Manag Subst use Subst use Disord pregnancy*. 2014.

7. National Institute on Alcohol Abuse and Alcoholism. Rethinking drinking: Alcohol and your health. 2010.

8. National Institute on Alcohol Abuse and Alcoholism. Beyond hangovers: Understanding alcohol's impact on your health. 2010.

9. Surgeon Generol of the United States of America. Surgeon General's advisory on alcohol use in pregnancy. 2005. http://come-over.to/FAS/SurGenAdvisory.htm.

10. National Institute on Alcohol Abuse and Alcoholism. NIAAA council approves definition of binge drinking. *NIAAA Newsletter*. 2004:3.

11. World Health Organization. *The ICD-10 Classification of Mental and Behavioural Disorders Diagnostic Criteria for Research*. Geneva; 1992.

12. American Psychiatric Association. *Diagnostic and Statistical Manuel of Mental Disorders - Text Revision (DSM-IV)*. 5th text r. Washington DC; 2013.

13. Parry C, Patra J, Rehm J. Alcohol consumption and non-communicable diseases: epidemiology and policy implications. *Addiction*. 2011;106(10):1718-1724. doi:10.1111/j.1360-0443.2011.03605.x.

14. Schmidt L, Mäkelä P, Rehm J, Room R. *Alcohol: Equity and Social Determinants*. Vol 11. World Health Organization; 2010.

15. Babor T. *Alcohol: No Ordinary Commodity: Research and Public Policy*. Oxford University Press; 2010.

16. Collins S. Associations between socioeconomic factors and alcohol outcomes. *Alcohol Res Curr Rev*. 2016;38(1):83-94.

17. Schuckit M. Alcohol use disorders. *Lancet*. 2009;373(9662):492-501.

18. Wilsnack S, Wilsnack R, Kantor L. Focus on: Women and the cost of alcohol use. *Alcohol Res Curr Rev*. 2013;35(2):219-228.

19. Probst C, Roerecke M, Behrendt S, Rehm J. Socioeconomic differences in alcohol-attributable mortality compared with all-cause mortality: a systematic review and meta-analysis. *Int J Epidemiol*. 2014;43(4):1314-1327.

20. Probst C, Roerecke M, Behrendt S, Rehm J. Gender differences in socioecenomic inequality of alcohol-attributable mortality: A systematic review and meta-analysis. *Drug Alcohol Rev*. 2015;34(3):267-277.

21. Room R, Jernigan D, Carlini-Marlatt B, et al. Alcohol in developing societies: a public health approach. *Finnish Found Alcohol Stud*. 2002.

22. Delker E, Brown Q, Hasin D. Alcohol consumption in demographic subpopulations: An epidemiologic overview. *Alcohol Res Curr Rev*. 2016;38(1):7-15.

23. Chartier K, Vaeth P, Caetano R. Focus on: Ethnicity and the social and health harms from drinking. *Alcohol Res*. 2013;35(2):229-237.

24. Blas E, Kurup A. *Equity, Social Determinants and Public Health Programmes*. World Health Organization; 2010.

25. Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *Lancet*. 2009;373(9682):2223-2233.

26. Lim S, Vos T, Flaxman A, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease study 2010. *Lancet*. 2012;380(9859):2224-2260.

27. Mayosi B, Fisher A, Lalloo U, Sitas F, Tollman S, Bradshaw D. The burden of non-communicable diseases in South Africa. *Lancet*. 2009;374(9693):934-947.

28. Mayosi B, Lawn J, van Niekerk A, et al. Health in South Africa: changes and challenges since 2009. *Lancet*. 2012;380(9858):2029-2043.

29. Schneider M, Norman R, Parry C, Bradshaw D, Plüddemann A. Estimating the burden of disease attributable to alcohol use in South Africa in 2000. *South African Med J*. 2007;97(8):664-672.

30. Ramsoomar L, Morojele N. Trends in alcohol prevalence, age of initiation and association with alcohol related harm among South African youth: implications for policy. *South African Med J*. 2012;102(7):609-612.

31. Matzopoulos R, Truen S, Bowman B, Corrigall J. The cost of harmful alcohol use in South Africa. *South African Med J*. 2014;104(2):127-132.

32. Dolk H, Loane M, Garne E. The prevalence of congenital anomalies in Europe. *Rare Dis Epidemiol*. 2010:349-364.

33. Christianson A, Howson CP, Modell B, others. March of Dimes: global report on birth defects, the hidden toll of dying and disabled children. *March Dimes Glob Rep birth defects, hidden toll dying Disabl Child*. 2005.

34. Lui L, Johnson H, Cousens S, et al. Global, regional and national causes of child mortality: an updated systematic analyses for 2010 with time trends since 2000. *Lancet*. 2012;379(9832):2151-2161.

35. Modell B, Berry R, Boyle C, et al. Global, regional and national causes of child mortality. *Lancet*. 2012;380(9853):1556.

36. Lui L, Cousens S, Lawn J, Black R. Global, regional and national causes of child mortality - Author's reply. *Lancet*. 2012;380(9853):1556-1557.

37. Omran AR. The Epidemiologic Transition: A Theory of the Epidemiology of Population Change. *Milbank Mem Fund Q*. 1971;49(4):509-538. http://www.jstor.org/stable/3349375.

38. Malherbe H, Christianson A, Aldous C. Need for services for the care and preventio of congenital disorders in South Africa as the country's epidemiological transition evolves. *South African Med J*. 2015;105(3):186-188.

39. World Health Orginization. Sixty-third World Health Assembly adopts resolutions on MDGs, infant feeding, pneumonia, and birth defects. 2010. http://www.who.int/maternal_child_adolescent/news_events/news/2010/17_5_10/en/.

40. Wilsnack R, Wilsnack S, Obot I. Why study gender, alcohol and culture? In: *Alcohol, Gender and Drinking Problems: Perspectives from Low and Middle Income Countries*. Geneva: World Health Organization; 2005.

41. Grucza R, Bucholz K, Rice J, Bierut L. Secular trends in the lifetime prevalence of alcohol dependence in the United States: a re-evaluation. *Alcohol Clin Exp Res*. 2008;32(5):763-

770.

42. Bloomfield K, Gmel G, Neve R, Mustonen H. Investigating gender convergence in alcohol consumption in Finland, Germany, The Netherlands, and Switzerland: A repeated survey analysis. *Subst Abus*. 2001;22:39-53.

43. Kuntsche S, Gmel G, Knibbe R, et al. Gender and cultural differences in the association between family roles, social stratification, and alcohol use: a European cross-cultural analysis. *Alcohol Alcohol*. 2006;41(1):i37-i46.

44. Parry C, Plüddemann A, Steyn K, Bradshaw D, Norman R, Laubscher R. Alcohol use in South Africa: findings from the first Demographic and Health Survey (1998). *J Stud Alcohol*. 2005;66(1):91-97.

45. Department of Health and Medical Research Council. South Africa Demographic and Health Survey, 2003. Department of Health. http://www.mrc.ac.za/bod/sadhs.htm. Published 2007. Accessed September 12, 2016.

46. Peltzer K, Ramlagan S. Alcohol use trends in South Africa. *J Soc Sci*. 2009;18(1):1-12.

47. Peltzer K, Davids A, Njuho P. Alcohol use and problem drinking in South Africa: findings from a national population-based survey. *Afr J Psychiatry*. 2011;14(1):30-37.

48. Gossage JP, Snell CL, Parry CDH, et al. Alcohol use, working conditions, job benefits, and the legacy of the "Dop" system among farm workers in the Western Cape Province, South Africa: Hope despite high levels of risky drinking. *Int J Environ Res Public Health*. 2014;11(7):7406-7424.

49. Shisana O, Rehle T, Simbayi L, et al. South African National HIV Prevalence, Incidence and Behaviour Survey, 2012. 2014.

50. Kalichman S, Simbayi L, Kaufman M, Cain D, Jooste S. Alcohol use and sexual risks for HIV/AIDS in sub-Saharan Africa: systematic review of empirical findings. *Prev Sci*. 2007;8(2):141.

51. Baliunas D, Rehm J, Irving H, Shuper P. Alcohol consumption and risk of incident human immunodeficiency virus infection: A meta-analysis. *Int J Public Health*. 2010;55(3):159-166.

52. Kader R, Seedat S, Govender R, Koch JR, Parry CD. Hazardous and harmful use of alcohol and/or other drugs and health status among South African patients attending HIV clinics. *AIDS Behav*. 2014;18(3):525-534.

53. Armstrong E, Abel E. Fetal alcohol syndrome: the origins of a moral panic. *Alcohol Alcohol*. 2000;35(3):276-282.

54. Serdula M, Williamson D, Kendrick J, Anda R, Byers T. Trends in alcohol consumption by pregnant women 1985 through 1988. *JAMA*. 1991;265(7):876-879.

55. Floyd R, Weber M, Denny C, O'Connor M. Prevention of fetal alcohol spectrum disorders. *Dev Disabil Res Rev*. 2009;15(3):193-199.

56. Floyd R, Decouflé P, Hungerford D. Alcohol use prior to pregnancy recognition. *Am J Prev Med*. 1999;17(2):101-107.

57. Substance Abuse and Mental Health Services Administration. *The NSDUH Report: Substance Use among Women during Pregnancy and Following Childbirth*. Rockville MD; 2010.

58. Ethen M, Ramadhani T, Scheuerle A, et al. National Birth Defects Prevention Study. Alcohol consumption by women before and during pregnancy. *Matern Child Health J*. 2009;13(2):274-285.

59. Balachova T, Sobell LC, Agrawal S, et al. Using a single binge drinking question to identify Russian women at risk for an alcohol-exposed pregnancy. *Addict Behav*. 2015;46:53-57.

60. Tan C, Denny C, Cheal N, Sniezek J, Kanny D. Alcohol use and binge drinking among women of childbearing age - United States, 2011-2013. *MMWR Morb Mortal Wkly rep*. 2015;64(37):1042-1046.

61. Tenkku LE, Morris DS, Salas J, Xaverius PK. Racial disparities in pregnancy-related drinking reduction. *Matern Child Health J*. 2009;13(5):604.

62. Fortin M, Muckle G, Anassour-Laouan-Sidi E, Jacobson SW, Jacobson JL, Bélanger RE. Trajectories of alcohol use and binge drinking among pregnant Inuit women. *Alcohol Alcohol*. 2016;51(3):339-346.

63. Croxford J, Viljoen D. Alcohol consumption by pregnant women in the Western Cape. *S Afr Med J*. 1999;89(9):962-965.

64. Petersen Williams P, Jordaan E, Mathews C, Lombard C, Parry C. Alcohol and other drug use during pregnancy among women attending midwife obstetric units in the Cape Metropole, South Africa. *Adv Prev Med*. 2014;(2014).

65. Louw J, Peltzer K, Matseke G. Prevalence of alcohol use and associated factors in pregnant antenatal care attendees in Mpumalanga, South Africa. *J Psychol Africa*. 2011;21(4):565-572.

66. Desmond K, Milburn N, Richter L, et al. Alcohol consumption among HIV-positive pregnant women in KwaZulu-Natal, South Africa: prevalence and correlates. *Drug Alcohol Depend*. 2012;120(1):113-118.

67. Brittain K, Remien RH, Phillips T, et al. Factors associated with alcohol use prior to and during pregnancy among HIV-infected pregnant women in Cape Town, South Africa. *Drug Alcohol Depend*. 2017;173:69-77.

68. Isaksen A, Østbye T, Mmbaga B, Daltveit A. Alcohol consumption among pregnant women in Northern Tanzania 2000-2010: a registry-based study. *BMC Pregnancy Childbirth*. 2015;15(1):205.

69. Lemione P, Harasseau H, Borteryu JP, Menuet JC. Les enfants de parents alcooliques: anomalies observ{é}es {à} propos de 127 cas [The children of alcoholic parents: anomalies observed in 127 cases]. *Quest Medicale*. 1968;21.

70. Jones K, Smith D, Ulleland C, Streissguth A. Pattern of malformation in offspring of chronic alcoholic mothers. *Lancet*. 1973;301(7815):1267-1271.

71. Jones K, Smith D. Recognition of the fetal alcohol syndrome

in early infancy. *Lancet*. 1973;302(7836):999-1001.

72. Stratton K, Howe C, Battaglia FC, et al. *Fetal Alcohol Syndrome: Diagnosis, Epidemiology, Prevention, and Treatment*. National Academies Press; 1996.

73. Astley S, Clarren S. Measuring the facial phenotype of individuals with prenatal alcohol exposure: correlations with brain dysfunction. *Alcohol Alcohol*. 2001;36(2):147-159.

74. Hoyme HE, May PA, Kalberg WO, et al. A practical clinical approach to diagnosis of fetal alcohol spectrum disorders: clarification of the 1996 institute of medicine criteria. *Pediatrics*. 2005;115(1):39-47.

75. Friedman J. How do We Know if an Exposure is Actually Teratogenic in Humans?. *Am J Med Genet Part C Semin Med Genet*. 2011;157(3):170-174.

76. Sulik K. Genesis of alcohol-induced craniofacial dysmorphism. *Exp Biol Med*. 2005;230(6):366-375.

77. Wilson J. Principles of teratology. In: *Environment and Birth Defects*. New York: Academic Press; 1973:11-34.

78. Maier S, West J. Drinking Patterns and alcohol-related birth defects. *Alcohol Res Heal*. 2001;25(3):168-174.

79. Martin R, Jones K, Benirschke K. Absence of the lateral philtral ridges: a clue to the structural basis of the philtrum. *Am J Med Genet*. 1996;65(2):117-123.

80. Nunez C, Roussotte F, Sowell E. Focus on: structural and functional brain abnormalities in fetal alcohol spectrum disorders. *Alcohol Res Heal*. 2011;34(1):121-131.

81. Baily B, Sokol R. Prenatal alcohol exposure and miscarriage, stillbirth, preterm delivery, and sudden infant death syndrome. *Alcohol Reserach Heal*. 2011;34(1):86.

82. Bonthuis D, West J. Alcohol-Induced Neuronal Loss in Developing Rats: Increased Brain Damage with Binge Exposure. *Alcohol Clin Exp Res*. 1990;(14):107-118.

83. Streissguth A, Barr H, Sampson P, Bookstein F. Prenatal alcohol and offspring development: the first fourteen years. *Drug Alcohol Depend*. 1994;36(2):89-99.

84. Jacobson J, Jacobson S, Sokol R, Ager J. Relation of maternal age and pattern of pregnancy drinking to functionally significant cognitive deficit in infancy. *Alcohol Clin Exp Res*. 1998;22(2):345-351.

85. Paintner A, Williams A, Burd L. Fetal alcohol spectrum disorders – implications for child neurology, Part 2: Diagnosis and Management. *J Child Neurol*. 2012;27(3):355-362.

86. Streissguth A, Barr H, Olson H, Sampson P, Bookstein F, Burgess D. Drinking During Pregnancy Decreases Word Attack and Arithmetic Scores on Standardized Tests: Adolescent Data From a Population-Based Prospective Study. *Alcohol Clin Exp Res*. 1994;18:248-254.

87. Lewis S, Zuccolo L, Davey -Smith G, et al. Fetal alcohol exposure and IQ at age 8: evidence from a population-based birth-cohort study. *PLoS One*. 2012;7(11):e49407.

88. Viljoen D, Carr L, Foroud T, Brooke L, Ramsay M, Li T. Alcohol dehydrogenase-2*2 allele is associated with decreased prevalence of fetal alcohol syndrome in the mixed-ancestry population of the Western Cape Province, South Africa. *Alcohol Clin Exp Res*. 2001;25(12):1719-1722.

89. Goodlett C, Horn K. Mechanisms of alcohol induced damage to the developing nervous system. *Alcohol Res Heal*. 2001;25(3):175-184.

90. Jones K. The effects of alcohol on fetal development. *Birth Defects Res Part C Embryo Today Rev*. 2011;93(1):3-11.

91. May PA, Hamrick K, Corbin K, et al. Dietary intake, nutrition, and fetal alcohol spectrum disorders in the Western Cape Province of South Africa. *Reprod Toxicology*. 2014;46:31-39.

92. Patra J, Bakker R, Irving H, Jaddoe VW V, Malini S, Rehm J. Dose--response relationship between alcohol consumption before and during pregnancy and the risks of low birthweight, preterm birth and small for gestational age (SGA)—a

systematic review and meta-analyses. *BJOG An Int J Obstet Gynaecol*. 2011;118(12):1411-1421.

93. Aase J. Clinical recognition of FAS: difficulties of detection and diagnosis. *Alcohol Res Heal*. 1994;18(1):5.

94. Sampson PD, Bookstein FL, Barr HM, Streissguth AP. Prenatal alcohol exposure, birthweight, and measures of child size from birth to age 14 years. *Am J Public Health*. 1994;84(9):1421-1428.

95. Astley SJ, Clarren SK. A case definition and photographic screening tool for the facial phenotype of fetal alcohol syndrome. *J Pediatr*. 1996;129(1):33-41.

96. Jones KL, Hoyme HE, Robinson LK, et al. Fetal alcohol spectrum disorders: extending the range of structural defects. *Am J Med Genet Part A*. 2010;152(11):2731-2735.

97. Coles CD, Gailey AR, Mulle JG, Kable JA, Lynch ME, Jones KL. A comparison among 5 methods for the clinical diagnosis of fetal alcohol spectrum disorders. *Alcohol Clin Exp Res*. 2016;40(5):1000-1009.

98. May PA, Gossage JP, Smith M, et al. Population differences in dysmorphic features among children with fetal alcohol spectrum disorders. *J Dev Behav Pediatr JDBP*. 2010;31(4):304.

99. May PA, Tabachnick BG, Gossage JP, et al. Maternal risk factors predicting child physical characteristics and dysmorphology in fetal alcohol syndrome and partial fetal alcohol syndrome. *Drug Alcohol Depend*. 2011;119(1):18-27.

100. Streissguth AP, Barr HM, Sampson PD, Darby BL, Martin DC. IQ at age 4 in relation to maternal alcohol use and smoking during pregnancy. *Dev Psychol*. 1989;25(1):3.

101. Mattson SN, Crocker N, Nguyen TT. Fetal alcohol spectrum disorders: neuropsychological and behavioral features. *Neuropsychol Rev*. 2011;21(2):81-101.

102. Coles CD, Brown RT, Smith IE, Platzman KA, Erickson S, Falek A. Effects of prenatal alcohol exposure at school age. I.

Physical and cognitive development. *Neurotoxicol Teratol*. 1991;13(4):357-367.

103. Brown R, Coles C, Smith I, et al. Effects of prenatal alcohol exposure at school age. II. Attention and behavior. *Neurotoxicol Teratol*. 1991;13(4):369-376.

104. Howell KK, Lynch ME, Platzman KA, Smith GH, Coles CD. Prenatal alcohol exposure and ability, academic achievement, and school functioning in adolescence: a longitudinal follow-up. *J Pediatr Psychol*. 2006;31(1):116-126.

105. Mattson SN, Riley EP. A review of the neurobehavioral deficits in children with fetal alcohol syndrome or prenatal exposure to alcohol. *Alcohol Clin Exp Res*. 1998;22(2):279-294.

106. Mattson SN, Riley EP, Gramling L, et al. Heavy prenatal alcohol exposure with or without physical features of fetal alcohol syndrome leads to IQ deficits. *J Pediatr*. 1997;131(5):718-721.

107. Kodituwakku PW. Neurocognitive profile in children with fetal alcohol spectrum disorders. *Dev Disabil Res Rev*. 2009;15(3):218-224.

108. Rasmussen C. Executive functioning and working memory in fetal alcohol spectrum disorder. *Alcohol Clin Exp Res*. 2005;29(8):1359-1367.

109. Adnams C, Kodituwakku P, Hay A, Molteno C, Viljoen D, May P. Patterns of cognitive-motor development in children with fetal alcohol syndrome from a community in South Africa. *Alcohol Clin Exp Res*. 2001;25(4):557-562.

110. Coles CD, Platzman KA, Raskind-Hood CL, Brown RT, Falek A, Smith IE. A comparison of children affected by prenatal alcohol exposure and attention deficit, hyperactivity disorder. *Alcohol Clin Exp Res*. 1997;21(1):150-161.

111. Crocker N, Vaurio L, Riley EP, Mattson SN. Comparison of adaptive behavior in children with heavy prenatal alcohol exposure or attention-deficit/hyperactivity disorder. *Alcohol Clin Exp Res*. 2009;33(11):2015-2023.

112. Ware AL, Glass L, Crocker N, et al. Effects of Prenatal Alcohol Exposure and Attention-Deficit/Hyperactivity Disorder on Adaptive Functioning. *Alcohol Clin Exp Res*. 2014;38(5):1439-1447.

113. Mattson SN, Roesch SC, Fagerlund Å, et al. Toward a neurobehavioral profile of fetal alcohol spectrum disorders. *Alcohol Clin Exp Res*. 2010;34(9):1640-1650.

114. Mattson SN, Roesch SC, Glass L, et al. Further development of a neurobehavioral profile of fetal alcohol spectrum disorders. *Alcohol Clin Exp Res*. 2013;37(3):517-528.

115. Streissguth AP, Barr HM, Kogan J, Bookstein FL. Understanding the occurrence of secondary disabilities in clients with fetal alcohol syndrome (FAS) and fetal alcohol effects (FAE). *Final Rep to Centers Dis Control Prev*. 1996:6-96.

116. Grantham-McGregor S, Cheung YB, Cueto S, et al. Developmental potential in the first 5 years for children in developing countries. *Lancet*. 2007;369(9555):60-70.

117. Walker SP, Wachs TD, Gardner JM, et al. Child development: risk factors for adverse outcomes in developing countries. *Lancet*. 2007;369(9556):145-157.

118. May PA, Tabachnick BG, Gossage JP, et al. Maternal factors predicting cognitive and behavioral characteristics of children with fetal alcohol spectrum disorders. *J Dev Behav Pediatr JDBP*. 2013;34(5):314.

119. Kable JA, O'Connor MJ, Olson HC, et al. Neurobehavioral disorder associated with prenatal alcohol exposure (ND-PAE): proposed DSM-5 diagnosis. *Child Psychiatry Hum Dev*. 2016;47(2):335-346.

120. Johnston M V, Ishida A, Ishida WN, Matsushita HB, Nishimura A, Tsuji M. Plasticity and injury in the developing brain. *Brain Dev*. 2009;31(1):1-10.

121. Reid N, Dawe S, Shelton D, et al. Systematic review of fetal alcohol spectrum disorder interventions across the life span. *Alcohol Clin Exp Res*. 2015;39(12):2283-2295.

122. Adnams C, Sorour P, Kalberg W, et al. Language and literacy outcomes from a pilot intervention study for children with fetal alcohol spectrum disorders in South Africa. *Alcohol*. 2007;41(6):403-414.

123. Paley B. Introduction: Fetal alcohol spectrum disorders—Shedding light on an unseen disability. *Dev Disabil Res Rev*. 2009;15(3):167-169.

124. Williams JF, Smith VC, and Committee on Substance Abuse. Fetal alcohol spectrum disorders. *Pediatrics*. 2015;136(5):e1395--e1406.

125. Peterson K. Biomarkers for alcohol use and abuse-a summary. *Alcohol Res Heal*. 2004;28(1):30.

126. Sobell LC, Sobell MB. Alcohol consumption measures. *Assess alcohol Probl A Guid Clin Res*. 2003;2:75-99.

127. Lake SL, Hill-Kapturczak N, Liang Y, et al. Assessing the validity of participant-derived compared to staff-derived values to compute a binge score. *Alcohol Alcohol*. 2015;50(4):413-419.

128. Del Boca FK, Darkes J. The validity of self-reports of alcohol consumption: state of the science and challenges for research. *Addiction*. 2003;98(s2):1-12.

129. Johnson TP. Sources of error in substance use prevalence surveys. *Int Sch Res Not*. 2014;2014.

130. Midanik LT. Validity of self-reported alcohol use: A literature review and assessment. *Br J Addict*. 1988;83(9):1019-1029.

131. Babor T, Higgins-Biddle J, Saunders J, Monteiro M. *The Alcohol Use Disorders Identification Test. Guidelines for Use in Primary Care*. 2nd ed.; 2001.

132. Bush K, Kivlahan D, McDonell M, Fihn S, Bradley K. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. *Arch Intern Med*. 1998;158(16):1789-1795.

133. Frank D, DeBenedetti AF, Volk RJ, Williams EC, Kivlahan

DR, Bradley KA. Effectiveness of the AUDIT-C as a screening test for alcohol misuse in three race/ethnic groups. *J Gen Intern Med*. 2008;23(6):781-787.

134. Chang G. Alcohol-screening instruments for pregnant women. *Alcohol Res*. 2001;25(3):204-209.

135. Sobell LC, Sobell MB. Timeline Followback: A Technique for Assessing Self Reported Ethanol Consumption. Vol. 17. 1992.

136. Annis H, Sobell L, Ayala-Velazquez, H Rybakowski J, et al. Drinking-related assessment instruments: cross-cultural studies. *Subst Use Misuse*. 1996;31(11-12):1525-1546.

137. Sobell LC, Agrawal S, Annis H, et al. Cross-cultural evaluation of two drinking assessment instruments: alcohol timeline followback and inventory of drinking situations. *Subst Use Misuse*. 2001;36(3):313-331.

138. Viljoen D, Croxford J, Gossage JP, Kodituwakku PW, May PA. Characteristics of mothers of children with fetal alcohol syndrome in the Western Cape Province of South Africa: a case control study. *J Stud Alcohol*. 2002;63(1):6-17.

139. Viljoen DL, Gossage JP, Brooke L, et al. Fetal alcohol syndrome epidemiology in a South African community: a second study of a very high prevalence area. *J Stud Alcohol*. 2005;66(5):593-604.

140. May PA, Gossage JP, Marais A-S, et al. The epidemiology of fetal alcohol syndrome and partial FAS in a South African community. *Drug Alcohol Depend*. 2007;88(2):259-271.

141. Jacobson SW, Jacobson JL, Sokol RJ, Martier SS, Ager JW, Kaplan MG. Maternal recall of alcohol, cocaine, and marijuana use during pregnancy. *Neurotoxicol Teratol*. 1991;13(5):535-540.

142. Hannigan JH, Chiodo LM, Sokol RJ, et al. A 14-year retrospective maternal report of alcohol consumption in pregnancy predicts pregnancy and teen outcomes. *Alcohol*. 2010;44(7):583-594.

143. Astley S, Clarren S. Diagnosing the full spectrum of fetal

alcohol exposed individuals: introducing the 4-Digit Diagnostic Code. *Alcohol Alcohol*. 2000;35(4):400-410.

144. Bertrand J, Floyd L, Weber M. *Fetal Alcohol Syndrome. Guidelines for Referral and Diagnosis*.; 2004.

145. Chudley A, Conry J, Cook J, Loock C, Rosales T, LeBlanc N. Fetal alcohol spectrum disorder: Canadian guidelines for diagnosis. *Can Med Assoc J*. 2005;172(5suppl):S1-S21.

146. Cook JL, Green CR, Lilley CM, et al. Canada Fetal Alcohol Spectrum Disorder Research Network.(2016). Fetal alcohol spectrum disorder: A guideline for diagnosis across the lifespan. *Can Med Assoc J*. 2016;188:191-197.

147. Hoyme HE, Kalberg WO, Elliott AJ, et al. Updated clinical guidelines for diagnosing fetal alcohol spectrum disorders. *Pediatrics*. 2016;138(2):e20154256.

148. Astley SJ. Comparison of the 4-digit diagnostic code and the Hoyme diagnostic guidelines for fetal alcohol spectrum disorders. *Pediatrics*. 2006;118(4):1532-1545.

149. Ceccanti M, Fiorentino D, Coriale G, et al. Maternal risk factors for fetal alcohol spectrum disorders in a province in Italy. *Drug Alcohol Depend*. 2014;145:201-208.

150. Petković G, Barišić I. Prevalence of fetal alcohol syndrome and maternal characteristics in a sample of schoolchildren from a rural province of Croatia. *Int J Environ Res Public Health*. 2013;10(4):1547-1561.

151. May PA, Baete A, Russo J, et al. Prevalence and characteristics of fetal alcohol spectrum disorders. *Pediatrics*. 2014;134(5):855-866.

152. May PA, Blankenship J, Marais A-S, et al. Approaching the prevalence of the Full Spectrum of Fetal Alcohol Spectrum Disorders in a South African population-based study. *Alcohol Clin Exp Res*. 2013;37(5):818-830.

153. Hoyme HE, Hoyme DB, Elliott AJ, et al. A South African mixed race lip/philtrum guide for diagnosis of fetal alcohol spectrum disorders. *Am J Med Genet Part A*. 2015;167(4):752-

755.

154. Jones KL. Early recognition of prenatal alcohol effects: A pediatrician's responsibility. 1999.

155. Little BB, Snell LM, Rosenfeld CR, Gilstrap LC, Gant NF. Failure to recognize fetal alcohol syndrome in newborn infants. *Am J Dis Child*. 1990;144(10):1142-1146.

156. Clarren SK, Randels SP, Sanderson M, Fineman RM. Screening for fetal alcohol syndrome in primary schools: a feasibility study. *Teratology*. 2001;63(1):3-10.

157. Stoler JM, Holmes LB. Under-recognition of prenatal alcohol effects in infants of known alcohol abusing women. *J Pediatr*. 1999;135(4):430-436.

158. May PA, Fiorentino D, Coriale G, et al. Prevalence of children with severe fetal alcohol spectrum disorders in communities near Rome, Italy: new estimated rates are higher than previous estimates. *Int J Environ Res Public Health*. 2011;8(6):2331-2351.

159. Moberg DP, Bowser J, Burd L, Elliott AJ, Punyko J, Wilton G. Fetal alcohol syndrome surveillance: age of syndrome manifestation in case ascertainment. *Birth Defects Res Part A Clin Mol Teratol*. 2014;100(9):663-669.

160. Cordero J, Tosca M, Falek A, Coles C, Smith I, Fernhoff P. The sensitivity of surveillance systems in detecting fetal alcohol syndrome (FAS) and alcohol related defects. In: *Proceedings of Greenwood Genetics Center*. ; 1990:88.

161. Hymbaugh K, Miller LA, Druschel CM, Podvin DW, Meaney FJ, Boyle CA. A multiple source methodology for the surveillance of fetal alcohol syndrome—the fetal alcohol syndrome surveillance network (FASSNet). *Teratology*. 2002;66(S1).

162. Lebese V, Aldous C, Malherbe HL. South African congenital disorders data, 2006-2014. *SAMJ South African Med J*. 2016;106(10):992-995.

163. Abel EL. Fetal alcohol syndrome: the "American Paradox."

Alcohol Alcohol. 1998;33(3):195-201.

164. May PA, Hymbaugh KJ, Aase JM, Samet JM. Epidemiology of fetal alcohol syndrome among American Indians of the Southwest. *Soc Biol*. 1983;30(4):374-387.

165. May PA, Gossage JP. Estimating the prevalence of fetal alcohol syndrome: A summary. *Alcohol Res Heal*. 2001;25(3):159-167.

166. Roozen S, Peters G-JY, Kok G, Townend D, Nijhuis J, Curfs L. Worldwide Prevalence of Fetal Alcohol Spectrum Disorders: A Systematic Literature Review Including Meta-Analysis. *Alcohol Clin Exp Res*. 2016;40(1):18-32.

167. May PA, Brooke L, Gossage JP, et al. Epidemiology of fetal alcohol syndrome in a South African community in the Western Cape Province. *Am J Public Health*. 2000;90(12):1905.

168. Centres for disease Control. Fetal alcohol syndrome--South Africa, 2001. *MMWR Morb Mortal Wkly Rep*. 2003;52(28):660.

169. Burd L, Cox C, Poitra B, et al. The FAS Screen: a rapid screening tool for fetal alcohol syndrome. *Addict Biol*. 1999;4(3):329-336.

170. Elliott EJ, Payne J, Morris A, Haan E, Bower C. Fetal alcohol syndrome: a prospective national surveillance study. *Arch Dis Child*. 2008;93(9):732-737.

171. Fitzpatrick JP, Latimer J, Carter M, et al. Prevalence of fetal alcohol syndrome in a population-based sample of children living in remote Australia: The Lililwan Project. *J Paediatr Child Health*. 2015;51(4):450-457.

172. Petković G, Barišić I. FAS prevalence in a sample of urban schoolchildren in Croatia. *Reprod Toxicol*. 2010;29(2):237-241.

173. May PA, Fiorentino D, Phillip Gossage J, et al. Epidemiology of FASD in a province in Italy: Prevalence and characteristics of children in a random sample of schools. *Alcohol Clin Exp*

Res. 2006;30(9):1562-1575.

174. Haynes G, Dunnagan T, Christopher S. Determinants of alcohol use in pregnant women at risk for alcohol consumption. *Neurotoxicol Teratol*. 2003;25(6):659-666.

175. Skagerström J, Chang G, Nilsen P. Predictors of drinking during pregnancy: a systematic review. *J women's Heal*. 2011;20(6):901-913.

176. Beijers C, Burger H, Verbeek T, Bockting C, Ormel J. Continued smoking and continued alcohol consumption during early pregnancy distinctively associated with personality. *Addict Behav*. 2014;39(5):980-986.

177. Morojele NK, London L, Olorunju SA, Matjila MJ, Davids AS, Rendall-Mkosi KM. Predictors of risk of alcohol-exposed pregnancies among women in an urban and a rural area of South Africa. *Soc Sci Med*. 2010;70(4):534-542.

178. O'Connor MJ, Tomlinson M, LeRoux IM, Stewart J, Greco E, Rotheram-Borus MJ. Predictors of alcohol use prior to pregnancy recognition among township women in Cape Town, South Africa. *Soc Sci Med*. 2011;72(1):83-90.

179. Paintner A, Williams AD, Burd L. Fetal alcohol spectrum disorders—implications for child neurology, part 1: prenatal exposure and dosimetry. *J Child Neurol*. 2012;27(2):258-263.

180. May PA, Gossage J. Maternal risk factors for fetal alcohol spectrum disorders: not as simple as it might seem. *Alcohol Res Heal*. 2011;34(1):15.

181. Christoffel KK, Salafsky I. Fetal alcohol syndrome in dizygotic twins. *J Pediatr*. 1975;87(6):963-967.

182. Zakhari S. Overview: how is alcohol metabolized by the body? *Alcohol Res Heal*. 2006;29(4):245-255.

183. Anthenelli R, Grandison L. Effects of stress on alcohol consumption. *Alcohol Res Curr Rev*. 2012;34(4):381.

184. Keyes K, Hatzenbuehler M, Grant B, Hasin D. Childhood trauma, PTSD, and alcohol dependence. *Alcohol Res*.

2012;34(4):408-413.

185. Petrakis IL, Gonzalez G, Rosenheck R, Krystal JH. Comorbidity of Alcholism and Psychiatric Disorders: An Overview. *Alcohol Res*. 2002;26(2):81.

186. Frankenberger DJ, Clements-Nolle K, Yang W. The association between adverse childhood experiences and alcohol use during pregnancy in a representative sample of adult women. *Women's Heal issues*. 2015;25(6):688-695.

187. Kvigne VL, Leonardson GR, Borzelleca J, Brock E, Neff-Smith M, Welty TK. Characteristics of mothers who have children with fetal alcohol syndrome or some characteristics of fetal alcohol syndrome. *J Am Board Fam Pract*. 2003;16(4):296-303.

188. Ennett ST, Foshee VA, Bauman KE, et al. The social ecology of adolescent alcohol misuse. *Child Dev*. 2008;79(6):1777-1791.

189. Rosenquist JN, Murabito J, Fowler JH, Christakis NA. The spread of alcohol consumption behavior in a large social network. *Ann Intern Med*. 2010;152(7):426-433.

190. Lorant V, Nicaise P. Binge drinking at University: a social network study in Belgium. *Health Promot Int*. 2014:dau007.

191. Borsari B, Carey KB. Descriptive and injunctive norms in college drinking: a meta-analytic integration. *J Stud Alcohol*. 2003;64(3):331-341.

192. Abel EL, Hannigan JH. Maternal risk factors in fetal alcohol syndrome: provocative and permissive influences. *Neurotoxicol Teratol*. 1995;17(4):445-462.

193. Chiodo LM, Da Costa DE, Hannigan JH, et al. The impact of maternal age on the effects of prenatal alcohol exposure on attention. *Alcohol Clin Exp Res*. 2010;34(10):1813-1821.

194. Dewing S, Tomlinson M, le Roux IM, Chopra M, Tsai AC. Food insecurity and its association with co-occurring postnatal depression, hazardous drinking, and suicidality among women in peri-urban South Africa. *J Affect Disord*. 2013;150(2):460-

465.

195. Scorgie F, Blaauw D, Dooms T, Coovadia A, Black V, Chersich M. “I get hungry all the time”: experiences of poverty and pregnancy in an urban healthcare setting in South Africa. *Global Health*. 2015;11(1):37.

196. May PA, Gossage JP, White-Country M, et al. Alcohol consumption and other maternal risk factors for fetal alcohol syndrome among three distinct samples of women before, during, and after pregnancy: the risk is relative. In: *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*. Vol 127. ; 2004:10-20.

197. May PA, Hamrick KJ, Corbin KD, et al. Maternal nutritional status as a contributing factor for the risk of fetal alcohol spectrum disorders. *Reprod Toxicol*. 2016;59:101-108.

198. Chavez GF, Cordero JF, Becerra JE. Leading major congenital malformations among minority groups in the United States, 1981-1986. *MMWR CDC Surveill Summ Morb Mortal Wkly report CDC Surveill Summ Dis Control*. 1988;37(3):17.

199. Lee CS, Colby SM, Rohsenow DJ, López SR, Hernández L, Caetano R. Acculturation stress and drinking problems among urban heavy drinking Latinos in the Northeast. *J Ethn Subst Abuse*. 2013;12(4):308-320.

200. Chae DH, Takeuchi DT, Barbeau EM, et al. Alcohol disorders among Asian Americans: associations with unfair treatment, racial/ethnic discrimination, and ethnic identification (the national Latino and Asian Americans study, 2002--2003). *J Epidemiol Community Health*. 2008;62(11):973-979.

201. Blume AW. Advances in substance abuse prevention and treatment interventions among racial, ethnic, and sexual minority populations. *Alcohol Res Curr Rev*. 2016;38(1):47.

202. Chartier KG, Scott DM, Wall TL, et al. Framing ethnic variations in alcohol outcomes from biological pathways to neighborhood context. *Alcohol Clin Exp Res*. 2014;38(3):611-618.

203. Gordis E. Alcohol and minorities: an update. *Alcohol Alert*.

2002;55:1-4.

204. Beauvais F. American Indians and alcohol. *Alcohol Res Heal*. 1998;22(4):253.

205. Wall TL, Luczak SE, Hiller-Sturmhöfel S. Biology, genetics, and environment: Underlying factors influencing alcohol metabolism. *Alcohol Res Curr Rev*. 2016;38(1):59.

206. Khaole NCO, Ramchandani VA, Viljoen DL, Li T. A pilot study of alcohol exposure and pharmacokinetics in women with or without children with fetal alcohol syndrome. *Alcohol Alcohol*. 2004;39(6):503-508.

207. Geronimus A, Hicken M, Keene D, Bound J. "Weathering" and age patterns of allostatic load scores among black and whites in the United States. *Am J Public Health*. 2006;96(5):826-833. doi:doi:10.2105/AJPH.2004.060749.

208. Holzman C, Eyster J, Kleyn M, et al. Maternal weathering and risk of preterm delivery. *Am J Public Health*. 2009;99(10):1864-1971.

209. Habbick BF, Nanson JL, Snyder RE, Casey RE, Schulman AL. Foetal alcohol syndrome in Saskatchewan: unchanged incidence in a 20-year period. *Can J public Heal Rev Can sante publique*. 1995;87(3):204-207.

210. Barry K, Caetano R, Chang G, et al. Reducing Alcohol-Exposed Pregnancies: A Report of the National Task Force on Fetal Alcohol Syndrome and Fetal Alcohol Effect. US Public Service Task Force. https://www.cdc.gov/ncbddd/fasd/documents/redalcohpreg.pdf . Published 2009. Accessed February 7, 2017.

211. Sudhinaraset M, Wigglesworth C, Takeuchi DT. Social and cultural contexts of alcohol use: Influences in a social--ecological framework. *Alcohol Res Curr Rev*. 2016;38(1):35.

212. Kaskutas LA, Graves K. Relationship between cumulative exposure to health messages and awareness and behavior-related drinking during pregnancy. *Am J Heal Promot*. 1994;9(2):115-124.

213. Hankin JR, Sloan JJ, Firestone IJ, Ager JW, Sokol RJ, Martier SS. A time series analysis of the impact of the alcohol warning label on antenatal drinking. *Alcohol Clin Exp Res*. 1993;17(2):284-289.

214. Hankin JR, Firestone IJ, Sloan JJ, Ager JW, Sokol RJ, Martier SS. Heeding the alcoholic beverage warning label during pregnancy: multiparae versus nulliparae. *J Stud Alcohol*. 1996;57(2):171-177.

215. Glik D, Halpert-Schilt E, Zhang W. Narrowcasting risks of drinking during pregnancy among African American and Latina adolescent girls. *Health Promot Pract*. 2001;2(3):222-232.

216. Glik D, Prelip M, Myerson A, Eilers K. Fetal alcohol syndrome prevention using community-based narrowcasting campaigns. *Health Promot Pract*. 2008;9(1):93-103.

217. Krans EE, Davis MM, Schwarz EB. Psychosocial risk, prenatal counseling and maternal behavior: findings from PRAMS, 2004-2008. *Am J Obstet Gynecol*. 2013;208(2):141--e1.

218. Holder HD. Community prevention of alcohol problems. *Addict Behav*. 2000;25(6):843-859.

219. Rotheram-Borus MJ, Tomlinson M, Le Roux I, Stein JA. Alcohol use, partner violence, and depression: a cluster randomized controlled trial among urban South African mothers over 3 years. *Am J Prev Med*. 2015;49(5):715-725.

220. Babor TF, McRee BG, Kassebaum PA, Grimaldi PL, Ahmed K, Bray J. Screening, Brief Intervention, and Referral to Treatment (SBIRT) toward a public health approach to the management of substance abuse. *Subst Abus*. 2007;28(3):7-30.

221. Stade BC, Bailey C, Dzendoletas D, Sgro M, Dowswell T, Bennett D. Psychological and/or educational interventions for reducing alcohol consumption in pregnant women and women planning pregnancy. *Cochrane Libr*. 2009.

222. Kaner EFS, Dickinson HO, Beyer F, et al. The effectiveness of brief alcohol interventions in primary care settings: a

systematic review. *Drug Alcohol Rev*. 2009;28(3):301-323.

223. Savage CL, Sanchez M. Alcohol and Substance Use Disorder Screening, Brief Intervention, and Referral to Treatment Among People Living With HIV/AIDS. *J Addict Nurs*. 2016;27(3):214-217.

224. Wilton G, Moberg DP, Van Stelle KR, Dold LL, Obmascher K, Goodrich J. A randomized trial comparing telephone versus in-person brief intervention to reduce the risk of an alcohol-exposed pregnancy. *J Subst Abuse Treat*. 2013;45(5):389-394.

225. Floyd RL, Sobell M, Velasquez MM, et al. Preventing alcohol-exposed pregnancies: a randomized controlled trial. *Am J Prev Med*. 2007;32(1):1-10.

226. Chang G. Screening and brief intervention in prenatal care settings. *Alcohol Res Heal*. 2004;28(2):80.

227. Rendall-Mkosi K, Morojele N, London L, Moodley S, Singh C, Girdler-Brown B. A randomized controlled trial of motivational interviewing to prevent risk for an alcohol-exposed pregnancy in the Western Cape, South Africa. *Addiction*. 2013;108(4):725-732.

228. Popova S, Lange S, Burd L, Rehm J. The economic burden of fetal alcohol spectrum disorder in Canada in 2013. *Alcohol Alcohol*. 2015:agv117.

229. Credé S, Sinanovic E, Adnams C, London L. The utilization of health care services by children with Foetal Alcohol Syndrome in the Western Cape, South Africa. *Drug Alcohol Depend*. 2011;115(3):175-182.

230. Tomlinson M, O'Connor MJ, Le Roux IM, et al. Multiple risk factors during pregnancy in South Africa: the need for a horizontal approach to perinatal care. *Prev Sci*. 2014;15(3):277-282.

231. Jonsson E, Salmon A, Warren KR. The international charter on prevention of fetal alcohol spectrum disorder. *Lancet Glob Heal*. 2014;2(3):e135--e137.

232. Goldstein S. What needs to be done to end South Africa's

status as a nation of heavy drinkers? The Conversation. http://theconversation.com/what-needs-to-be-done-to-end-south-africas-status-as-a-nation-of-heavy-drinkers-43567. Published 2015. Accessed February 6, 2017.

233. de Wit E, Delport W, Rugamika CE, et al. Genome-wide analysis of the structure of the South African Coloured Population in the Western Cape. *Hum Genet*. 2010;128(2):145-153.

234. Falletisch LA. Understanding the legacy of dependency and powerlessness experienced by farm workers on wine farms in the Western Cape. Doctoral dissertation. Stellenbosch: University of Stellenbosch , 2008.

235. London L. The dop'system, alcohol abuse and social control amongst farm workers in South Africa: a public health challenge. *Soc Sci Med*. 1999;48(10):1407-1414.

236. London L. Alcohol consumption amongst South African farm workers: a challenge for post-apartheid health sector transformation. *Drug Alcohol Depend*. 2000;59(2):199-206.

237. te Water NJ, London L, Pitt B, Mahomed C. The'dop'system around Stellenbosch--results of a farm survey. *South African Med journal= Suid-Afrikaanse Tydskr vir Geneeskd*. 1998;88(9):1102-1105.

238. London L. Human rights, environmental justice, and the health of farm workers in South Africa. *Int J Occup Environ Health*. 2003;9(1):59-68.

239. Viall J, James WG, Gerwel J. *Grape: Stories of the Vineyards in South Africa:[from Slavery to BEE 1652-2011]*. Tafelberg; 2011.

240. Kehler J. Women and poverty: the South African experience. *J Int Womens Stud*. 2013;3(1):41-53.

241. Mphi M. Female alcoholism problems in Lesotho. *Addiction*. 1994;89(8):945-949.

242. Statistics South Africa. Census 2011 in brief. Statistics South Africa.

https://www.statssa.gov.za/Census2011/Products/Census_2011_Census_in_brief.pdf. Published 2012. Accessed July 25, 2014.

243. Coovadia H, Jewkes R, Barron P, Sanders D, McIntyre D. The health and health system of South Africa: historical roots of current public health challenges. *Lancet*. 2009;374(9692):817-834.

244. London L. Health of Farm Workers in South Africa. *Int J Occup Environ Health*. 2003;9(1):59-68.

245. Centers for Disease Control. CDC clinical growth charts. http://www.cdc.gov/growthcharts/. Published 2000. Accessed September 27, 2014.

246. Nellhaus G. Head circumference from birth to eighteen years. *Pediatrics*. 1968;41(1):106-114.

247. Griffiths R. *The Ability of Young Children: A Comprehensive System of Mental Measurement for the First Eight Years of Life*. Test Agency for ARICD; 1984.

248. Griffiths R. The abilities of babies: a study in mental measurement. 1954.

249. Cockcroft K, Amod Z, Soellaart B. Level of maternal education and performance of Black, South African infants on the 1996 Griffiths Mental Development Scales: original article. *Afr J Psychiatry*. 2008;11(1):44-50.

250. Luiz DM, Foxcroft CD, Tukulu AN. The Denver II Scales and the Griffiths scales of mental development: A correlational study. *J Child Adolesc Ment Health*. 2004;16(2):77-81.

251. Davies L, Dunn M, Chersich M, et al. Developmental delay of infants and young children with and without fetal alcohol spectrum disorder in the Northern Cape Province, South Africa. *Afr J Psychiatry*. 2011;14(4):298-305.

252. Luiz D, Barnard A, Knoesen N, et al. Griffiths Mental Development Scales: Extended Revised. Two to eight years. Administration Manual. *Hogrefe, Oxford, UK*. 2006.

253. Ivens J, Martin N. A common metric for the Griffiths Scales. *Arch Dis Child*. 2002;87(2):109-110.

254. Beck AT, Ward CH, Mendelson M, Mock J, ERBAUGH J. An inventory for measuring depression. *Arch Gen Psychiatry*. 1961;4(6):561-571.

255. Ward CL, Flisher AJ, Zissis C, Muller M, Lombard C. Reliability of the beck depression inventory and the self-rating anxiety scale in a sample of South African adolescents. *J Child Adolesc Ment Health*. 2003;15(2):73-75.

256. Gardner JB. Should drinking during pregnancy be criminalised to prevent fetal alcohol spectrum disorder? *South African J Bioeth Law*. 2016;9(1):26-30.

257. Malet L, Llorca P-M, Boussiron D, Schwan R, Facy F, Reynaud M. General practitioners and alcohol use disorders: quantity without quality. *Alcohol Clin Exp Res*. 2003;27(1):61-66.

258. Adhikari M. "God made the white man, God made the black man...": popular racial stereotyping of coloured people in apartheid South Africa. *South African Hist J*. 2006;55(1):142-164.

259. Blume AW, Lovato L V, Thyken BN, Denny N. The relationship of microaggressions with alcohol use and anxiety among ethnic minority college students in a historically White institution. *Cult Divers Ethn Minor Psychol*. 2012;18(1):45.

260. Ellison GT, De Wet T. The use of'racial'categories in contemporary South African health research. A survey of articles published in the South African Medical Journal between 1992 and 1996. *South African Med journal= Suid-Afrikaanse Tydskr vir Geneeskd*. 1997;87(12):1671-1679.

261. Cheung YW. Approaches to ethnicity: Clearing roadblocks in the study of ethnicity and substance use. *Int J Addict*. 1993;28(12):1209-1226.

262. Nghe LT, Mahalik JR, Lowe SM. Examining Traditional Gender Roles, the Refugee Experience. *J Multicult Couns Devel*. 2003;31:4.

263. Evans-Campbell T. Historical trauma in American Indian/Native Alaska communities: A multilevel framework for exploring impacts on individuals, families, and communities. *J Interpers Violence*. 2008;23(3):316-338.

264. May PA, de Vries MM, Marais A-S, et al. The continuum of fetal alcohol spectrum disorders in four rural communities in South Africa: prevalence and characteristics. *Drug Alcohol Depend*. 2016;159:207-218.

265. Kvigne VL, Leonardson GR, Borzelleca J, Neff-Smith M, Welty TK. Characteristics of children whose siblings have fetal alcohol syndrome or incomplete fetal alcohol syndrome. *Pediatrics*. 2009;123(3):e526--e533.

266. Autti-Rämö I, Fagerlund Å, Ervalahti N, Loimu L, Korkman M, Hoyme HE. Fetal alcohol spectrum disorders in Finland: clinical delineation of 77 older children and adolescents. *Am J Med Genet Part A*. 2006;140(2):137-143.

267. Kalberg WO, May PA, Blankenship J, Buckley D, Gossage JP, Adnams CM. A practical testing battery to measure neurobehavioral ability among children with FASD. *Int J Alcohol Drug Res*. 2013;2(3):51.

268. Grantham-McGregor S, Committee ICD, others. Early child development in developing countries. *Lancet*. 2007;369(9564):824.

269. Balachova T, Bonner B, Chaffin M, et al. Women's alcohol consumption and risk for alcohol-exposed pregnancies in Russia. *Addiction*. 2012;107(1):109-117.

270. Mengel MB, Searight HR, Cook K. Preventing alcohol-exposed pregnancies. *J Am Board Fam Med*. 2006;19(5):494-505.

271. Prince N, Knoetze D. Pregnant Moms "Deliberately Binge Drinking." Lifestyle/Parenting. iol.co.za/lifestyle/parenting/pregnant-moms-deliberately-binge-drinking-1449012. Published 2013. Accessed December 14, 2015.

272. Venkataramani AS, Maughan-Brown B, Nattrass N, Ruger JP.

Social grants, welfare, and the incentive to trade-off health for income among individuals on HAART in South Africa. *AIDS Behav*. 2010;14(6):1393-1400.

273. Goldblatt B. Gender and social assistance in the first decade of democracy: a case study of South Africa's Child Support Grant. *Polit South African J Polit Stud*. 2005;32(2):239-257.

274. Watt MH, Eaton LA, Choi KW, et al. "It's better for me to drink, at least the stress is going away": Perspectives on alcohol use during pregnancy among South African women attending drinking establishments. *Soc Sci Med*. 2014;116:119-125.

275. Kott A. Rates of unintended pregnancy remain high in developing regions. *Int Perspect Sex Reprod Health*. 2011;37(1):46.

276. Cannon MJ, Dominique Y, O'Leary LA, Sniezek JE, Floyd RL. Characteristics and behaviors of mothers who have a child with fetal alcohol syndrome. *Neurotoxicol Teratol*. 2012;34(1):90-95.

277. Esper LH, Furtado EF. Identifying maternal risk factors associated with Fetal Alcohol Spectrum Disorders: a systematic review. *Eur Child Adolesc Psychiatry*. 2014;23(10):877-889.

278. May PA, Gossage JP, Brooke LE, et al. Maternal risk factors for fetal alcohol syndrome in the Western cape province of South Africa: a population-based study. *Am J Public Health*. 2005;95(7):1190-1199.

279. Bingol N, Schuster C, Fuchs M, et al. The influence of socioeconomic factors on the occurrence of fetal alcohol syndrome. *Adv Alcohol Subst Abuse*. 1987;6(4):105-118.

280. Myers B, Kline TL, Doherty IA, Carney T, Wechsberg WM. Perceived need for substance use treatment among young women from disadvantaged communities in Cape Town, South Africa. *BMC Psychiatry*. 2014;14(1):100.

281. Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and

adults during 1980--2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2014;384(9945):766-781.

282. Kruger HS, Puoane T, Senekal M, van der Merwe M-T. Obesity in South Africa: challenges for government and health professionals. *Public Health Nutr*. 2005;8(5):491-500.

283. Rahman MM, Abe SK, Kanda M, et al. Maternal body mass index and risk of birth and maternal health outcomes in low- and middle-income countries: a systematic review and meta-analysis. *Obes Rev*. 2015;16(9):758-770.

284. Meintjies H, Hall K, Sambu H. Demography of South Africa's Children. In: *South African Child Gauge*. ; 2015:102-106.

285. Astley SJ, Stachowiak J, Clarren SK, Clausen C. Application of the fetal alcohol syndrome facial photographic screening tool in a foster care population. *J Pediatr*. 2002;141(5):712-717.

286. Lange S, Shield K, Rehm J, Popova S. Prevalence of fetal alcohol spectrum disorders in child care settings: a meta-analysis. *Pediatrics*. 2013;132(4):e980--e995.

287. Ward C, Makusha T, Bray R. Parenting, poverty and young people in South Africa: What are the connections? *ChildGauge*. 2015:69.

288. Hutton HE, McCaul ME, Santora PB, Erbelding EJ. The relationship between recent alcohol use and sexual behaviors: gender differences among sexually transmitted disease clinic patients. *Alcohol Clin Exp Res*. 2008;32(11).

289. Flynn A, Wells S. Community indicators: assessing the impact of alcohol use on communities. *Alcohol Res Curr Rev*. 2014;35(2):135.

290. Azar M, Springer S, Meyer J, Altice F. A systematic review of the impact of alcohol use disorders on HIV treatment outcomes, adherence to antiretroviral therapy and health care utilization. *Drug Alcohol Depend*. 2010;112(3):178-193.

291. Statistics South Africa. Mid-year population estimates - 2015.

https://www.statssa.gov.za/publications/P0302/P03022015.pdf ,. Published 2016. Accessed December 23, 2016.

292. Parry CDH, Gossage JP, Marais A-S, et al. Comparison of baseline drinking practices, knowledge, and attitudes of adult s residing in communities taking part in the FAS prevention study in South Africa. *Afr J Drug Alcohol Stud*. 2012;11(2).

293. Babor TF, Jernigan D, Brookes C, Brown K. Toward a public health approach to the protection of vulnerable populations from the harmful effects of alcohol marketing. *Addiction*. 2017;112(S1):125-127.

294. Parry C, Burnhams NH, London L. A total ban on alcohol advertising: Presenting the public health case. *SAMJ South African Med J*. 2012;102(7):602-604.

295. Parry C, London L, Myers B. Delays in South Africa's plans to ban alcohol advertising. *Lancet*. 2014;383(9933):1972.

296. Jewkes R, Dunkle K, Nduna M, et al. Factors associated with HIV sero-status in young rural South African women: connections between intimate partner violence and HIV. *Int J Epidemiol*. 2006;35(6):1461-1468.

297. Caetano R. Acculturation, drinking and social settings among US Hispanics. *Drug Alcohol Depend*. 1987;19(3):215-226.

298. Caetano R, Ramisetty-Mikler S, Rodriguez LA. The Hispanic Americans Baseline Alcohol Survey (HABLAS): the association between birthplace, acculturation and alcohol abuse and dependence across Hispanic national groups. *Drug Alcohol Depend*. 2009;99(1):215-221.

299. Dee TS. Alcohol abuse and economic conditions: Evidence from repeated cross-sections of individual-level data. *Health Econ*. 2001;10(3):257-270.

300. Morojele NK, Kachieng'a MA, Mokoko E, et al. Alcohol use and sexual behaviour among risky drinkers and bar and shebeen patrons in Gauteng province, South Africa. *Soc Sci Med*. 2006;62(1):217-227.

301. Roozen S, Black D, Peters GJY, et al. Fetal Alcohol Spectrum

Disorders (FASD): an Approach to Effective Prevention. *Curr Dev Disord Reports*. 2016;3(4):229-234.

302. Padarath A, King J, Mackie E, Casciola J. South African Health Review. Health Systems Trust. http://www.hst.org.za/publications/south-african-health-review-2016. Published 2016. Accessed February 16, 2017.

303. Massyn N, Peer N, Padarath A, Barron P, Day C. District Health Barometer 2014/15. Durban: Health Systems Trust. http://www.hst.org.za/publications/district-health-barometer-201415-1. Published 2015. Accessed February 17, 2017.

304. Chersich MF, Blaauw D, Scorgie F, et al. Safeguarding maternal and child health in South Africa by starting the Child Support Grant before birth: design lessons from pregnancy support programmes in 27 countries: research. *South African Med J*. 2016;106(12):1192-1210.

305. of Obstetricians AC, Gynecologists, others. At-risk drinking and alcohol dependence: obstetric and gynecologic implications. *Comm Opin*. 2011;496:1-6.

306. Tomlinson M, Hartley M, Le Roux IM, Rotheram-Borus MJ. The Philani Mentor Mothers Intervention: neighbourhood wide impact on child growth in Cape Town's peri-urban settlements. *Vulnerable Child Youth Stud*. 2016;11(3):211-220.

307. O'Connor MJ, Rotheram-Borus MJ, Tomlinson M, Bill C, LeRoux IM, Stewart J. Screening for fetal alcohol spectrum disorders by nonmedical community workers. *J Popul Ther Clin Pharmacol J la Ther des Popul la pharamcologie Clin*. 2014;21(3):e442.

308. Montag AC, Brodine SK, Alcaraz JE, et al. Preventing Alcohol-Exposed Pregnancy Among an American Indian/Alaska Native Population: Effect of a Screening, Brief Intervention, and Referral to Treatment Intervention. *Alcohol Clin Exp Res*. 2015;39(1):126-135.

309. Hanson JD, Miller AL, Winberg A, Elliott AJ. Prevention of alcohol-exposed pregnancies among nonpregnant American Indian women. *Am J Heal Promot*. 2013;27(3 suppl):S66--

S73.

310. Calac D, Kolander C, Nyquist C. Creating a culturally appropriate web-based behavioral intervention for American Indian/Alaska Native women in Southern California: the healthy women healthy Native nation study. *Am Indian Alsk Native Ment Health Res*. 2013;20(1):1.

311. Montag A, Clapp JD, Calac D, Gorman J, Chambers C. A review of evidence-based approaches for reduction of alcohol consumption in Native women who are pregnant or of reproductive age. *Am J Drug Alcohol Abuse*. 2012;38(5):436-443.

LIST OF PUBLICATIONS

PEER REVIEWED FULL-LENGTH JOURNAL ARTICLES:

1. Davies L-A, Cockcroft K, Olinger L, Chersich M, **Urban M**, Chetty-Makkan CM, Turnbull OH, Olivier L, Viljoen D. Alcohol exposure during pregnancy alters childhood developmental trajectories in a rural South African community. Acta Paediatrica, epub ahead of print, July 2017 DOI:10.1111/apa.13978
2. Kinnear C; Glanzmann B; Banda E; Schlechter N; Durrheim G; Neethling A; Nel E; Schoeman M; Johnson G; van Helden PD; Hoal EG; Esser M; **Urban M**; Moller M. Exome sequencing identifies a novel TTC37 mutation in the first reported case of Trichohepatoenteric syndrome (THE-S) in South Africa. BMC Medical Genetics, accepted for publication
3. **Urban MF**, Olivier L, Louw J, Lombard C, Vijoen D, Scorgie F, Chersich M. Changes in drinking patterns during and after pregnancy among mothers of children with fetal alcohol syndrome: a study in three districts of South Africa. *Drug and Alcohol Dependence 2016, 168: 13-21.* http://dx.doi.org/10.1016/j.drugalcdep.2016.08.629
4. **Urban MF**, Olivier L, Viljoen D, Lombard C, Louw JG, Drotsky L-M, Temmerman M, Chersich MF. Prevalence of fetal alcohol syndrome in a South African city with a predominantly Black African population. *Alcohol: Clinical and Experimental Research 2015; 39(6):1016-26*. PMID: 25941030
5. Schoeman M, Esser MM, **Urban MF**. Living with X-linked Agammaglobulinemia (XLA) in a developing country setting: clinical and counselling considerations in an affected family. *Current Allergy and Clinical Immunology 2015. Current Allergy and Clinical Immunology 2015; 28:64-69.*
6. Roberts T, Chetty M, Stephen L, **Urban M**, Fieggen K, Beighton P. Rubinstein-Taybi syndrome: dental manifestations and management. South African Journal of Child Health 2014; 8(1) DOI:10.7196/sajch.569
7. Schoeman M, Apffelstaedt JP, Baatjes K, **Urban M**. Implementation of a breast cancer genetic service in South Africa – lessons learned. *South African Medical Journal* 2013; 103(8):529-533. DOI: 10.7196/SAMJ.6814. PMID: 23885733
8. Olivier L*, **Urban M***, Chersich MF, Temmerman M, Viljoen D. Burden of fetal alcohol spectrum disorders in the rural West Coast of South Africa. *South African Medical Journal 2013;*

*103(6): 402-405.*DOI:10.7196/SAMJ.6249. PMID: 23725961 (*Equal first author)
9. Dandara C, Scott C, **Urban M**, Fieggen K, Arendse R, Beighton P. Confirmation of the recurrent ACVR1 617G>A mutation in South Africans with fibrodysplasia ossificans progressiva. *South African Medical Journal* 2012; 102(7):631-3. PMID: 22748444.
10. Chersich MF, **Urban M**, Olivier L, Davies L, Chetty C, Viljoen D. Universal prevention is associated with lower prevalence of fetal alcohol spectrum disorder in Northern Cape, South Africa: a multicentre before-after study. *Alcohol and Alcoholism*, 2012; 47(1):67-74. PMID: 22037537
11. **Urban M**, Stewart C, Ruppelt T, Geerts L. Effectiveness of prenatal screening for Down syndrome on the basis of maternal age in Cape Town. *South African Medical Journal*, 2011; 101:45-48.
12. Boutall A, **Urban MF**, Stewart C. Diagnosis, etiology and outcome of fetal ascites at a South African Hospital. *International Journal of Obstetrics and Gynaecology* 2011; 115(2): 148-152.
13. Davies L, Dunn M, Chersich M, **Urban M**, Chetty C, Olivier L, Viljoen D. Developmental Delay of Infants and Young Children with and without fetal alcohol spectrum disorder in the Northern Cape Province, South Africa. *African Journal of Psychiatry* 2011; *14: 299-305.*
14. Roberts T, Stephen L, Scott C, **Urban M**, Sudi S, Beighton P. Fibrodysplasia ossificans progressive: dental implications in five cases. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology* 2011; 112(1):11-18.
15. Scott C, **Urban M**, Arendse R, Dandara C, Beighton P. Fibrodysplasia Ossificans Progressiva in South Africa: Difficulties in management in a developing country. *Journal of Clinical Rheumatology*, 2011; 17(1):37-41.
16. Venkatesh KK, de Bruyn G, Marinda E, Otowombe K, van Niekerk R, **Urban M**, Triche EW, McGarvey ST, Lurie MN, Gray G. Morbidity and mortality among infants born to HIV-infected women in South Africa: Implications for child health in resource-limited settings. *Journal of Tropical Paediatrics* 2011 57(2): 109-199. Doi:10.1093/tropj/fmq061. PMID 20601692.
17. **Urban M**, Chersich MF, Fourie L, Chetty C, Olivier L, Rosenthal J, Viljoen D. Fetal alcohol syndrome among grade-one children in the Northern Cape Province: prevalence and risk factors. *South African Medical Journal* 2008; 98(11): 877-882. PMID: 19177895

18. **Urban MF**, Bolton KD, Mokhachane M, Mphahlele RM, Bomela HN, Monaheng L, Beckh-Arnold E and Cooper P. Growth of infants born to HIV-infected women when fed a biologically acidified starter formula with and without probiotics. *South African Journal of Clinical Nutrition* 2008; 21(1):28-32.
19. Beighton P, Mennen U, Golele SS, **Urban MF**. Orthopaedic implications of heritable osteolysis in South Africa. *South African Orthopaedic Journal* 2007; 6(2):26-32.
20. Chersich MF, **Urban MF**, Venter FW, Wessels T, Krause A, Gray GE, Luchters S, Viljoen DL. Efavirenz use during pregnancy and for women of child-bearing potential. *AIDS Research and Therapy*. 2006; 7(3): 11. PMID: 22038428
21. Gray GE, **Urban M**, Chersich MF, Bolton C, van Niekerk R, Violari A, Stevens W, McIntyre JA; for the PEP study group. A randomised trial of two post-exposure prophylaxis regimens to reduce mother-to-child HIV-1 transmission in infants of untreated mothers. *AIDS* 2005; 19: 1289-1297. PMID: 16052084
22. Sherman GG, Jones SA, Coovadia AH**, Urban MF**, Bolton KD. PMTCT programme--partial assessments can build the picture. *South African Medical Journal* 2004; 94(12):934.
23. **Urban M**, Chersich M. Acceptability and utilisation of voluntary HIV testing and nevirapine to reduce mother-to-child transmission of HIV-1 integrated into routine clinical care. *South African Medical Journal*. 2004; 94(5):362-6. PMID: 15211956
24. Sherman GG, Jones SA, Coovadia AH, **Urban MF**, Bolton KD. PMTCT from research to reality--results from a routine service. *South African Medical Journal*. 2004; 94(4):289-92.

SCIENTIFIC LETTERS:

1. Horn A, Nel A, **Urban M**. Bilateral periventricular nodular heterotopias - neonatal cranial ultrasound. *South African Journal of Radiology*, 2010 (March): 13-14.
2. **Urban MF** and Chersich MF. Dandy-Walker variant in an infant prenatally exposed to antiretroviral medication. *South African Medical Journal*. 2007; 97(10):947-8.

EDITORIALS AND OPINION PIECES:

1. Southern African Society for Human Genetics (2016) Implications of direct-to-consumer whole-exome sequencing in South Africa. *South African Medical Journal 106: 139-140.*
2. **Urban M**. Genomics in Medicine: from promise to practice. *South African Medical Journal 2015; 105 (7):545-7.*

3. **Urban M**, Morris S, Schoeman M, Geerts L, Norman K. Appropriate clinical use of non-invasive prenatal testing in South Africa. *Obsteric and Gynecology Forum* 2014; 24(1): 35-40.
4. **Urban M**. Clinical issues in genetic testing for multifactorial diseases. *South African Medical Journal* 2013; 103(8): 517. DOI:10.7196/SAMJ.7232.
5. **Urban M**, Chersich MF. Update on the HIV and breastfeeding dilemma. PedMed November 2003: 3.
6. Karim SA, Karim QA, Adhikari M, Cassol S, Chersich M, Cooper P et al. Vertical HIV transmission in South Africa: translating research into policy and practice. Commentary: Lancet 2002, 359(9311): 992.

BOOK CHAPTERS:

1. **Urban M**. Human Genetics. In: Kruger H et al Eds, *Clinical Gynaecology,5th edition. Juta Publishers, Cape Town, South Africa* (2015). Accepted for publication
2. **Urban M**, Geerts L. Prenatal diagnostic services and prevention of birth defects in South Africa (2012). In: Kumar D, Ed, *Genomics and Health in the developing world, Oxford University Press, New York, USA, p547-567.ISBN-10:0-19-537475-4.*
3. Shreier AR, **Urban M**. Legislation affecting children in South Africa. In: Kibel M and Wagstaff L, Eds (1995). *Child Health for All: a manual for Southern Africa, 2nd Ed, Oxford University Press, Cape Town, South Africa, p379-84.*